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THE SUPERIORITY OF INOCULATIONS WITH MIXED TRIPLE VACCINE (B. TYPHOSUS, B. PARA-TYPHOSUS A, AND B. PARA-TYPHOSUS B)

OVER SUCCESSIVE INOCULATIONS WITH THE SINGLE VACCINES, AS SHOWN BY AGGLUTININ CURVES IN MEN AND RABBITS *

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PHILADELPHIA

At present the subject of immunity against the enteric fevers, that is, typhoid, paratyphoid A and paratyphoid B, is of the utmost importance. Records of the Franco-German War, of the Boer War,[1] of the Russo-Japanese War[2] and of the Spanish-American War[3] clearly show that the number of deaths from enteric fevers in those wars was approximately half of that due to wounds. Therefore, the problem of producing immunity against the enteric fevers has occupied the minds of many investigators. The success of the work done by Wright, Kabeshima[2] and others in regard to immunity against typhoid fever has been admirably demonstrated by its practical application in the armies of the United States, of Japan and of all the countries now at war (1917). It may safely be stated that since prophylactic vaccination against typhoid fever has been made more or less universal among armies, the losses from that disease have became practically negligible.[4]

During the present war the paratyphoid infections have assumed the preeminent place formerly held by typhoid, and consequently investigations were necessary to place these, likewise, under control by prophylactic vaccination. Castellani,[5] Cummins and Cumming,[6] Kabe-

* Alvarenga Prize Essay, 1917. Submitted for publication Sept. 1, 1917.

1. Osler, Sir William: Bacteria versus Bullets in Boer War.
2. Kabeshima T.: Ueber Typhus—und Paratyphus schutz-impfung mittels gemischter Typhus—und Paratyphus-vaccine und die Ergebnisse der Schuztimpfung in der Kaiserliche Japanischen Marine, etc. Centralbl. f. Bakteriol., etc., Orgl., 1914, **74,** 294.
3. Russell, F. F.: Am. Jour. Med. Sc., 1913, **146,** 803.
4. McQueeney, E. J.: Immunity against Infectious Disease, with Special Reference to Antityphoid Inoculation. Lancet, London, 1915, **1,** 265.
5. Castellani: Brit. Med. Jour., 1916, **1.**
6. Cummins, S. L., and Cumming, C. C.: Experiments on Immunization against Bacillus Paratyphosus A. Jour. Royal Army Med. Corps, **21,** 282.

shima,[2] Vincent, Dreyer,[1] Ainley Walker,[8] and others, have demonstrated the advantages of prophylactic vaccination with combined typhoid, paratyphoid A and paratyphoid B vaccines. Kabeshima[2] has not only shown that simultaneous inoculation with a vaccine containing equal parts of *B. typhosus, B. paratyphosus A and B. paratyphosus B* produced immunity against these three infections in man and animals, but he has also proved that the reaction to this so-called "triple vaccine" was not more severe than that due to typhoid vaccine alone. One of the problems in relation to prophylactic inoculation against the enteric fevers is whether or not a better immunity against these infections is obtained by inoculating with the three micro-organisms simultaneously, or by immunizing with each bacillus separately by means of a succession of inoculations; and in the latter case whether anything depends on the order in which the vaccines are introduced. It is in regard to this question as well as in regard to the course of the immunity (as measured by agglutinins) produced by prophylactic enteric vaccination, that, at Prof. George Dreyer's suggestion, I have performed, under the supervision of Dr. E. W. Ainley Walker, a series of immunization experiments in men and animals with *B. typhosus* and the paratyphoid bacillus.

It seemed probable that the alterations which occur in the amount of agglutinins present in the blood during different periods and modes of immunization could be made to yield fresh and valuable information as to what is taking place in the organism during immunization. Moreover, it was of considerable economic and general interest to ascertain as exactly as possible at what period the greatest amount of antibody is found present in the blood of inoculated animals.

For these reasons I carried out a series of inoculations in a number of men and rabbits with vaccines prepared from cultures of one, two or all three of the bacilli (*B. typhosus, B. paratyphosus A* and *B. paratyphosus B*), varying the order of their introduction in the successive immunizations of different groups of rabbits.

The arrangement of these groups is shown in Table 1, where the nature of the vaccine used on each occasion, the dosage and the intervals of time between successive inoculations are given. Reference is also made in each case to the corresponding agglutinin curve of the serum.

The object in view in Group I was to determine the amounts of agglutinins for each micro-organism produced by simultaneous inoculations with all three bacilli, namely, *B. tyhosus, B. paratyphosus A* and *B. paratyphosus B.*

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7. Dreyer, G.: Hospitalstid., 1906; Ibid., Brit. Med. Jour., 1904, **2,** 564; Ibid., Jour. Pathol. and Bacteriol., 1909, **13,** 332.

8. Dreyer, Ainly Walker and Gibson: Lancet, London, 1915, **1,** 324.

TABLE 1.—SCHEME OF EXPERIMENTS ON RABBITS (INTRAPERITONEAL INOCULATIONS)

Title of Experiment	Bacilli Inoculated	Fourth Day, Millions	Fifteenth Day, Millions	Seventieth Day, Millions	Eightieth Day, Millions
Group I Curves 1 and 2 Rabbits 1 and 2	B. typhosus.....	1,000	2,000	None	None
	B. paratyphosus A.....	500	1,000	None	None
	B. paratyphosus B.....	500	1,000	None	None
Group II Curves 3 and 4 Rabbits 3 and 4	B. typhosus.....	None	None	1,000	2,000
	B. paratyphosus A.....	500	1,000	None	None
	B. paratyphosus B.....	500	1,000	None	None
Group III Curves 5 and 6 Rabbits 5 and 6	B. typhosus.....	1,000	2,000	None	None
	B. paratyphosus A.....	None	None	500	1,000
	B. paratyphosus B.....	None	None	500	1,000
Group IV Curves 7 and 8 Rabbits 7 and 8	B. typhosus.....	None	None	1,000	2,000
	B. paratyphosus A.....	None	None	500	1,000
	B. paratyphosus B.....	None	None	500	1,000
Group V Curves 9 and 10 Rabbits 9 and 10	B. typhosus.....	500	None	None	None
	B. paratyphosus A.....	250	None	None	None
	B. paratyphosus B.....	250	None	None	None

The aim in Group II was, first, to determine the amounts of agglutinins produced by simultaneous inoculations with *B. paratyphosus A* and *B. paratyphosus B*, and secondly, to ascertain the effect of subsequent inoculation with *B. typhosus* (after an interval of seven weeks).

The object aimed at in Group III was, first, to determine the amounts of agglutinins produced by inoculations with *B. typhosus*, and second, to ascertain the effect of subsequent simultaneous inoculations with *B. paratyphosus A* and *B. paratyphosus B* (after an interval of seven weeks). Thus the procedure was exactly the reverse of that in Group II.

The aim in Group IV was to determine the amounts of agglutinins produced by simultaneous inoculations with *B. typhosus*, *B. paratyphosus A* and *B. paratyphosus B*. The procedure was the same as in Group I, except that the inoculations were made at a later date, being carried out on the same days as the second series of inoculations in Groups II and III.

The aim in Group V was to determine the amounts of agglutinins produced by a simultaneous inoculation with *B. typhosus*, *B. para-*

typhosus A and *B. paratyphosus B* in a dose of half the amount used in the first doses in Groups I and IV, and of the same amount as used in the first doses of Groups VI and IX in the curves for men.

In order that the results of all the experiments might be comparable, Group I received its inoculations on the same days as the first series of inoculations in Groups II and III; and Group IV received its inoculations on the same days as the second series of inoculations in Groups II and III.

As soon as the foregoing experiments were fully in train, and facility had been acquired in the use of the methods involved, I instituted an investigation along similar lines in man.

For this purpose I availed myself of the kindness of a number of friends who willingly placed themselves at my disposal for inoculation and repeated blood examinations. To them I am deeply indebted for the opportunity of extending this investigation to the human subject, and examining in detail the development of agglutinins in man in response to immunization.

The experiments in man may be divided into eight groups (that is, Groups VI-XIII). Tables 2 and 3 exhibit the details of the grouping, together with the dosage and character of the vaccine used on each occasion and the intervals between the doses. Reference is also given in each case to the corresponding agglutination curve of the serum.

TABLE 2.—Scheme of Experiments on Men (Subcutaneous Inoculation)

Title of Experiment	Bacilli Inoculated	Third Day, Millions	Thirteenth Day, Millions	Thirty-sixth Day, Millions	Forty-sixth Day, Millions
Group VI Curves 11 and 12 V. G. and J. G. J.	B. typhosus.....	500	1,000	None	None
	B. paratyphosus A.....	250	500	None	None
	B. paratyphosus B.....	250	500	None	None
Group VII Curves 13 and 14 R. D. R. and H. W. T.	B. typhosus.....	None	None	500	1,000
	B. paratyphosus A.....	250	500	None	None
	B. paratyphosus B.....	250	500	None	None
Group VIII Curves 15 and 16 T. P. and E. A. W.	B. typhosus.....	500	1,000	None	None
	B. paratyphosus A.....	None	None	250	500
	B paratyphosus B.....	None	None	250	500
Group IX Curves 17 and 18 F. H. M. and W. C. C.	B. typhosus.....	None	None	500	1,000
	B. paratyphosus A.....	None	None	250	500
	B. paratyphosus B.....	None	None	250	500

TABLE 3.—SCHEME OF EXPERIMENTS ON MEN *

Title of Experiment	Bacilli Inoculated	Previous Typhoid Immunization, Millions	One to Three Years Later, Millions	Eighteen Days Later, Millions
Group X Curves 19, 20, and 21 J. W., E. F. H. and E. H. N.	B. typhosus.....	(1) 500 (2) 1,000 (3) 1,000	500	1,000
	B. paratyphosus A....	None	250	500
	B. paratyphosus B....	None	250	500
Group XI Curves 22 and 23 A. D. G. and W. C. D.	B. typhosus.....	(1) 500 (2) 1,000 (2) 1,000	500	1,000
	B. paratyphosus A....	None	500	1,000
	B. paratyphosus B....	None	500	1,000

* These represent the intervals and doses of the majority of the individuals. The exact intervals and doses are given for each case under the individual curves.

The object in view in Groups VI-IX (Curves 11-18) was the same as that which has already been outlined for Groups I-IV in the series of rabbits, except that the doses used in the human subject were only half the amounts used for the rabbits.

The aim in Group X was to determine the amounts of agglutinins and the effect produced by simultaneous inoculations with *B. typhosus, B. paratyphosus A* and *B. paratyphosus B* in individuals immunized at least a year previously with two and three inoculations of *B. typhosus.*

Group XI differs from Group X only in that the individuals received larger doses of *B. paratyphosus A* and *B. paratyphosus B* after having been inoculated at least a year previously with typhoid vaccine. The aim in Group XI was to determine how the production of agglutinins was affected by this increased dosage.

It is generally agreed that the agglutinins produced by typhoid and paratyphoid inoculations are at any rate a rough measure of the degree of immunity induced against infection by these organisms.[9] No evidence has hitherto been recorded, so far as my knowledge goes, which would tend to demonstrate the possibility of the production of antibodies without a corresponding development of immunity. Moreover, it is known that in other cases (for example, that of diphtheria antitoxin) immunity may persist for a considerable period after all measurable amounts of antibodies have disappeared from the serum.

Accordingly, it is, in the present state of knowledge, assumed with confidence that the measure of agglutinins present in the serum forms

9. Castellani: Ztschr. f. Hyg., 1902, p. 1; Ibid., Centralbl. f. Bakteriol., 1909; Ibid., Brit. Med. Jour., 1913, **2**, 1577; 1914, **2**, 814; 1915, **2**,; 1916, **1**.

a conservative estimate of the degree of immunity acquired, and it is further assumed that an active increase or decrease in the agglutination titer of the serum is an indication of an increase or decrease in immunity.

It is not the purpose of the present investigation to inquire in detail into the nature of the processes involved in agglutination. Nevertheless, a brief summary of the work done along this line may be of value in helping to throw light on the bearing of the experiments here recorded.

Nearly twenty years ago it was shown by Nicolle[10] that the agglutination of bacteria depended on the formation of a compound between the agglutinating agent, or agglutinin, of the serum, and the agglutinable substance in the bacteria. After Bordet[11] and later Joos[12] had proved that the presence of salt is essential for agglutination, it has been customary to regard the process as a direct or indirect consequence of the union of these three substances (that is, salt, agglutinin and agglutinable substance). Gruber,[13] Neufield,[14] Bordet,[11] Ehrlich, Wassermann,[15] Kirstein, Bail,[16] Eisenberg,[17] Volk, Dreyer and Jex-Blake,[18] Ainley Walker[19] (1902), Dreyer and Ainley Walker[20] (1909) have all greatly advanced our knowledge of the essential characteristics of this process, and Ainley Walker[19] and later Dreyer and Ainley Walker,[20] and more recently McFarland[21] (1911), have shown that agglutinins are produced by the leukocytes and leukocyte-forming tissues of the body (notably the bone marrow).

It thus appears that the production of agglutinins is in close association with those tissues of the body whose activity appears to form the basis for the development of immunity.

METHODS

The vaccines used in these experiments were kindly made for me by Dr. E. W. Ainley Walker, from stock cultures of *B. typhosus, B. paratyphosus A* and *B. paratyphosus B,* grown on agar slopes in culture tubes for twenty-four

10. Nicolle: Ann. de l'Inst. Pasteur, 1898, **12,** 161; Nicolle and French: Ibid., 1902, **16,** 562.
11. Bordet: Ann. de l'Inst. Pasteur, 1896, **10,** 193; Ibid., 1900, **14,** 257.
12. Joos: Ztschr. f. Hyg. u. Infectionskrankh., 1901, **36,** 422; Ibid., 1902, **40,** 203.
13. Gruber: München. med. Wchnschr., 1899, **46,** 1329.
14. Neufeld: Ztschr. f. Hyg. u. Infectionskrankh., Leipsic, 1902, **40,** 54.
15. Wassermann: Ztschr. f. Hyg. u. Infectionskrankh., 1902, **42,** 267.
16. Bail: Prag. med. Wchnschr., 1901, **26,** 85.
17. Eisenberg: Ztschr. f. Hyg. u. Infectionskrankh., 1902, **40,** 155.
18. Dreyer, G., and Blake, Jex A.: Jour. Path. and Bacteriol., January, 1906, p. 1.
19. Ainley Walker, E. W.: Jour. Hyg., Cambridge, 1903, **3,** 52.
20. Dreyer and Ainley Walker: Jour. Pathol. and Bacteriol., 1909, **14,** 28.
21. McFarland, W. S.: Communications de L'Institut Sciothiapigne de L'Etat Danois.

hours at 37 C. The growth was then washed off with normal saline solution to which 0.5 per cent. of phenol had been added. Each bacillary suspension was killed by heating in a waterbath at 56 C. for thirty minutes, then gradually raising the temperature to 56 C. and maintaining it at that level for an hour. The suspensions were then proved sterile and counted by Wright's blood-film method. One vaccine was then made so that 1 c.c. contained 1,000 million *B. typhosus.* A second vaccine containing 500 million *B. paratyphosus A,* and 500 million *B. paratyphosus B* in 1 c.c., and a third vaccine containing 1,000 million *B. typhosus,* 500 million *B. paratyphosus A,* and 500 million *B. paratyphosus B* in 1 c.c. were made. In order that Castellani's results might be repeated, a fourth vaccine was made containing 1,000 million *B. typhosus,* 1,000 million *B. paratyphosus A* and 1,000 million *B. paratyphosus B* in 1 c.c.

The vaccines were distributed into small sterile glass vials and sealed up and kept in a cold store at 2 C. until required. One or two bottles from each batch were then finally tested for sterility by culture methods and also by injecting 2 c.c. into a rabbit and a guinea-pig.

The inoculation was made in the case of two rabbits (Group V) by intraperitoneal injections of 0.5 c.c. of vaccine. But as this proved to be too small a dose with which to demonstrate agglutinin curves clearly, it was decided to give all of the other rabbits intraperitoneal injections of 1 c.c. followed in from nine to fifteen days later by a second dose of 2 c.c. In the case of the men, 0.5 c.c. of the vaccine, followed at an interval of from nine to twenty days by 1 c.c., was injected subcutaneously at the back of the arm with the usual precautions.

For each test from 1 to 2 c.c. of blood was taken. In the case of the rabbit it was procured by the following routine: the ear was shaved, then sharply flicked and a few drops of xylol were dropped on it to dilate the vessels. A small amount of petrolatum was rubbed on the area over the vessel, which was then punctured with a sterilized needle and the blood was allowed to drop into a small sterile test tube. In the case of the men from 1 to 2 c.c. of blood was usually collected by inserting a small sterilized hypodermic needle into the median basilic vein at the bend of the elbow (the skin having been previously painted with iodin) and the blood was aspirated into a sterile syringe. The blood was then blown into a small sterile test tube. In a few instances blood was obtained by pricking the thumb or finger and collecting the blood in a Wright's capsule or in the ingenious and efficient Asheville capsule described by Lyon.[22]

In practice, when frequent bleedings are necessary, the former technic is preferable, for it is simpler and causes far less discomfort to the subject.

The blood thus collected is allowed to clot for an hour at room temperature. The clot is then loosened from the sides of the tube with a fine glass rod and the tube is placed in a cold store at 2 C. until tested. I have found that tests of the same serum at different periods within forty-eight hours give no appreciable change, but keeping for a longer time gives less accurate observations.

The tubes are then centrifuged for several minutes and the supernatant serum pipetted off and tested by Dreyer's[7] technic.

The description which follows is that issued by the Standards Laboratory of the Department of Pathology of this university on behalf of the Medical Research Committee.

1. *Technic.*—Take a stand containing fifteen agglutination tubes in three rows of five each, and a dilution tube.

With the proper dropping pipet measure out into the dilution tube 30 drops of normal saline solution (0.85 per cent. sodium chlorid, in distilled water; where the water supply is pure, tap water can be used instead of saline solution), by means of gentle pressure on the teat.

Wash the pipet with distilled water.

22. Lyon, Jr., M. W.: Jour. Am. Med. Assn., 1915, **65,** 1813.

Dry out the pipet with successive quantities of absolute alcohol, followed by successive quantities of ether, and get rid of the ether.

Take up the serum to be tested into the dried pipet. For the first examination measure out 30 drops of the serum into the dilution tube already containing the 30 drops of saline solution, thus obtaining a dilution of 1 in 2. Mix thoroughly.

Carefully wash out the pipet.

With the pipet measure out into each row of tubes as follows:

No. of Tube	Drops of Normal Saline Solution	Drops of Serum Dilution 1 in 2	
1	0	10	To each tube in Row 1 add 15 drops of *B. typhosus* standard agglutinable culture.
2	5	5	
3	8	2	To each tube in Row 2 add 15 drops of *B. paratyphosus A* standard agglutinable culture.
4	9	1	
5	10	0	To each tube in Row 3 add 15 drops of *B. paratyphosus B* standard agglutinable culture.

At each stage of the procedure the pipet is carefully washed and dried out with successive quantities of absolute alcohol followed by successive quantities of ether.

Shake each tube thoroughly in order from right to left; that is, beginning each row with the highest dilution.

Place the stand either for two hours in a water-bath at from 50 to 55 C. (not in dry air), or for eight hours in an incubator at 37 C. if traces of hemolysis are present.[23]

In Tube 1 of each row the serum acts in a dilution of 1 in 5
In Tube 2 of each row the serum acts in a dilution of 1 in 10
In Tube 3 of each row the serum acts in a dilution of 1 in 25
In Tube 4 of each row the serum acts in a dilution of 1 in 50

Tube 5 containing no serum, is the control against spontaneous agglutination.

If the limit of agglutination is not reached within this series, higher dilutions are followed out in a similar manner.

Thus, for example, 57 drops of normal saline solution plus 3 drops of a 1 in 10 serum dilution will give a serum dilution of 1 in 200, and, using the same quantities as before, one has the serum acting in dilutions of 1 in 500, 1 in 1,000, 1 in 2,500, and 1 in 5,000. And similarly for higher dilutions.

The tubes are examined after two hours at from 50 to 55 C., or eight hours at 37 C., followed by standing at room temperature for fifteen minutes. The reading is taken by comparing each tube in succession with the control tube, and is preferably made by means of artificial light against a black background.

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23. In the case of the rabbit's serum, I found that hemolysis was slightly more frequent than in human serum, so I tested all of the former in the incubator at 37 C. for eight hours, while all of the latter I examined in the more usual way in the water bath at from 50 to 55 C. for two hours. I may say that in several experiments in which I tested one sample of the same serum in the water bath at 55 C. for two hours, and a second sample in the incubator at 37 C. for eight hours, I found no discrepancy or difference in the titer of agglutination produced; so the results of the two procedures are comparable in every way.

If daylight is used, the tubes inspected should be partly shadowed by passing a finger up and down behind them.

The highest dilution in which marked agglutination (medium sized flocculi) without sedimentation can be detected by the naked eye is "standard agglutination."

It frequently happens that in a given series there is no tube which shows a degree of agglutination which we can accept as "standard" (S). For instance there may be a jump from total (T) in one tube to trace (tr) in the next—the serum in the former is too strong, that in the latter too weak to produce standard (S) agglutination. Evidently standard (S) agglutination would be given in a serum dilution intermediate between these two. How are we to judge where to "place" our standard? Experience shows that all the recognizable degrees of agglutination, from total to trace, may be tabulated as in the following scheme:

T = Total—complete agglutination, the supernatant fluid being absolutely clear and all of the bacteria being in the sediment at the bottom of the tube.
T = a point midway between T and T —.
T — = Total Minus—supernatant fluid contains large flocculi and sedimentation is also present.
T — = a point midway between T — and S +.
S + = Coarse Standard—*large* flocculi *without* sedimentation.
S + = a point midway between S + and S.
S = Standard—*medium* flocculi *without* sedimentation.
S = a point midway between S and S —.
S — = Fine Standard—*fine flocculi without* sedimentation.
S — = a point midway between S — and tr +.
tr + = Trace Plus—agglutination *plainly* visible to naked eye but not sufficiently well marked to see separate flocculi.
tr = Trace—agglutination just visible to the naked eye.

This scheme shows 12 degrees of agglutination which may bridge the space between total and trace at equal intervals. Such a scheme makes it easy to calculate the probable position of standard agglutination when it falls between two tubes. For instance, on the twenty-eighth day of Curve 12 I found that the typhoid agglutination in the series of tubes was as follows:

Tube 1		Tube 2	
1	T	1	
2,500		5,000	S —

Tube 1 shows more than standard agglutination and Tube 2 shows less than standard. Standard, therefore, must lie between Tubes 1 and 2, that is, between the dilutions $\frac{1}{2,500}$ and $\frac{1}{5,000}$. Assuming that the gradations in the scheme I have adopted are equal, since eight of these gradations occur between T and S —, then S would be placed as follows:

	1	2	3	4	5	6	7	8
T	*T*	T —	*T* —	S +	*S* +	S	*S*	S —
1						1		1
2,500						4,375		5,000

In other words, the dilution in which standard agglutination would occur is $\frac{1}{2,500} + \frac{6}{8}$ of the difference between $\frac{1}{2,500}$ and $\frac{1}{5,000}$; that is, $\frac{1}{2,500} + \frac{6}{8}$ of $\frac{1}{2,500}$; that is, $\frac{1}{2,500} + \frac{1}{1,875}$; that is, $\frac{1}{4,375}$ (when divided by the sensitivity factor of the agglutinable culture used, this equalled 541 "standard agglutinin units").

This arbitrary system may lead to slight error, but as it has the great advantage of being applicable to all cases and does not depend on any bias of the experimenter, I have adopted it.

When the standard degree of agglutination ("standard agglutination") occurs with standard agglutinable culture in a serum dilution of 1 in x, then x divided by the figure given on the label (sensitivity factor) of the standard agglutinable culture employed gives the number of "standard agglutinin units" contained in 1 c.c. of the serum examined.[24]

Thus, if standard agglutination occurs in a dilution of 1 in 1,000 and the number on the label is 2.5, then $\frac{1,000}{2.5}$, that is, 400, is the number of standard agglutinin units contained in 1 c.c. of the serum examined.

For uniformity and simplicity in recording results they should be expressed in standard agglutinin units.

In the curves the ordinates represent the number of standard agglutinin units. The abscissae represent the days on which examinations were made.

The standardized agglutinable cultures[7] used in this technic were those prepared by the standards laboratory of the Department of Pathology, Oxford, on behalf of the Medical Research Committee, and the description I have given of their mode of preparation and standardization is the one issued by that laboratory.

1. *Preparation.*—The bacillus (*B. typhosus, B. paratyphosus,* etc.) is grown for twenty-four hours at 37 C. in ordinary veal peptone bouillon[25] in large Erlenmeyer flasks partly filled (1 liter of bouillon in a one and a half liter flask).

Before use the flasks of bouillon are sterilized in the autoclave at 115 C. for not more than fifteen minutes, and are then tested for sterility by incubation at 37 C. for forty-eight hours.

They are inoculated with a few drops each from a twenty to twenty-four hours' old bouillon culture of the bacillus (*B. typhosus* or *B. paratyphosus,* etc.).

The culture used should be one which has been subcultivated daily in bouillon for one or two weeks (or longer). This continued subcultivation has the effect of increasing its agglutinability and diminishing any tendency to spontaneous agglutination.

At the end of twenty to twenty-four hours' growth at 37 C. the flasks are well shaken, and to each is added 0.1 per cent. (1 c.c. per liter) of commercial (40 per cent.) formaldehyd. They are again shaken and placed in a cold chamber in the dark at about 2 C.

At intervals on the same day and on subsequent days for four or five days the flasks are again thoroughly shaken and replaced at once in the cold chamber.

After three or four days they will be found to be absolutely sterilized. Should it happen that the bacterial suspension is not entirely homogeneous, it may be shaken for some hours in a mechanical shaker, or may finally be filtered through sterile cotton wool.

2. *Standardization.*—The process of standardization consists (*a*) in making up the killed culture to an opacity as nearly as possible identical with that of the standard agglutinable culture; (*b*) in measuring its agglutinability as compared with the standard agglutinable culture by the use of standard serum.

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24. The standard agglutinin unit is that amount of agglutinating serum which when made up to 1 c.c. volume with normal saline solution causes standard agglutination on being mixed with 1.5 c.c. of a particular standard agglutinable culture and maintained at 55 C. for two hours in a water bath, or at 37 C. for eight hours in an incubator, followed by fifteen minutes at room temperature.

25. The bouillon is titrated against phenolphthalein and two-thirds of that amount of sodium hydrate which would render it neutral to phenolphthalein is added before the final boiling and filtration.

(*a*) The killed culture is diluted to the required degree with normal saline solution, to which has been added 0.1 per cent. of commercial formaldehyd.

In making up the standard agglutinable culture issued, a constant opacity is secured by the use of a special apparatus (the diaphanometer).[26] But for ordinary purposes it will be found that reasonable accuracy is obtained by putting a measured quantity of killed culture and of standard agglutinable culture in two tubes of equal size and diameter and comparing the opacity against thin black lines ruled on a white background. Diluting fluid is added until the opacity of the killed culture is brought down to that of the standard agglutinable culture. The quantity of fluid thus added being known, the amount of diluting fluid which must be added to the killed cultures is readily calculated.

(*b*) To measure the agglutinability of the killed culture thus diluted, proceed as follows:

Take two stands and place twelve agglutination tubes in each. Prepare (1) a dilution of standard agglutinating serum of such strength that each cubic centimeter contains from 4 to 8 standard agglutinin units, and from this prepare (2) a second dilution of half that strength.

With the pipet measure out:

	Drops of Normal Saline Solution	Serum Dilution
Into Tube 1 of each stand.....	0	10 drops of Dilution 1
Into Tube 2 of each stand.....	2	8 drops of Dilution 1
Into Tube 3 of each stand.....	4	6 drops of Dilution 1
Into Tube 4 of each stand.....	5	5 drops of Dilution 1
Into Tube 5 of each stand.....	6	4 drops of Dilution 1
Into Tube 6 of each stand.....	3	7 drops of Dilution 2
Into Tube 7 of each stand.....	4	6 drops of Dilution 2
Into Tube 8 of each stand.....	5	5 drops of Dilution 2
Into Tube 9 of each stand.....	6	4 drops of Dilution 2
Into Tube 10 of each stand.....	7	3 drops of Dilution 2
Into Tube 11 of each stand.....	8	2 drops of Dilution 2
Into Tube 12 of each stand.....	10	0 drops of Dilution 2

To each tube of one stand is added 15 drops of standard agglutinable culture, and to each tube of the other stand, 15 drops of the killed culture under standardization.

At each stage of the procedure the pipet is carefully washed and dried out with successive quantities of absolute alcohol, followed by successive quantities of ether.

The stands are placed for two hours in a water bath at from 50 to 55 C., then allowed to stand for fifteen minutes at room temperature and a reading subsequently taken by selecting in the series made with standard agglutinable culture the tube which exhibits standard agglutination (the highest dilution in which marked agglutination, without sedimentation, can be detected by the naked eye), and ascertaining which tube in the other series shows the same degree of agglutination. Should the tube be the same in each series the agglutinability of the killed culture is clearly equal to that of the standard. If not the same, the degree of agglutinability of the killed culture is now readily determined.

Thus, suppose that Tube 5 in the standard series corresponds to Tube 2 in the other series. The standard agglutinable culture is twice as agglutinable

26. More recently the standards department of the Department of Pathology, Oxford University, has adopted a more simple method of standardizing the opacity of agglutinable cultures. This is described by Dreyer and Gardner in *The Bio-Chemical Journal* (England), 1916, **10,** 399.

as the killed culture under standardization, since only half the quantity of serum has been required to agglutinate it to the same degree.

Hence, if any given serum presented for examination is found to agglutinate this particular killed culture in a dilution of, say, 1 in 500, then 500 multiplied by 2 and divided by the figure given on the label of the standard agglutinable culture is the number of standard agglutinin units in 1 c.c. of the serum examined.

Or again, if the killed culture were, say, 1.3 times as agglutinable as the standard agglutinable culture, then in the same example as above, 500 divided by 1.3, and again divided by the figure given on the label of the standard agglutinable culture, is the number of standard agglutinin units in 1 c.c. of the serum examined.

It will be seen from this description that the standard cultures are prepared in batches, each of which bears a different sensitivity factor by means of which the standard units are calculated. In working out long curves it is seldom possible to employ the same batch of culture throughout. In most of my curves one or more culture changes have been made. As a rule, no appreciable irregularity in the curve is found at these points, but in one or two instances a distinct irregularity occurred which was attributed to an alteration since the time of standardization in the sensitiveness of one or other of the cultures employed. When it has been perfectly clear that irregularities have been due to these changes, I have corrected the levels of the curve at these points.

CURVES PLOTTED FROM THE EXPERIMENTS ON MEN AND ANIMALS

I shall first give a more or less detailed description of the curves plotted from the results of agglutination tests made at short intervals on the rabbits, and then a similar description for the curves plotted from the agglutination tests made on the human subject.

The rabbits were all healthy animals. They were weighed daily. In each case the blood was examined two or more times before inoculations were commenced, to determine the base-line of normal agglutination. The local and general reactions to the inoculations given were in no way severe. At the most there was only a small decrease in body weight following the injection.

Rabbit 1.—(Group 1, Curve 1.) *The typhoid agglutinins* began their rise on the third day from inoculation, reaching a maximum on the ninth day. On the eleventh day the rapid fall of the typhoid agglutinins (33 per cent.) had begun. The second inoculation was then administered. For the next two days there is no change in agglutination titer (that is, no negative phase[27] was

27. Any fall in titer which occurs within forty-eight hours after an inoculation, is referred to in these descriptions of curves, as a negative phase. In many cases (as in falling curves) it might be contended that these drops were not the true negative phases of Wright. However, their significance will be discussed later.

EXPLANATION OF CURVES

——— = typhoid ——— = paratyphoid A - - - - - = paratyphoid B.

CURVE 1.—GROUP 1, RABBIT 1

Bacilli Inoculated	Fourth Day	Fifteenth Day	[illegible]	[illegible]
B. typhosus	1,000 million	2,000 million	Nil.	Nil.
B. paratyphosus A	500 million	1,000 million	Nil.	Nil.
B. paratyphosus B	500 million	1,000 million	Nil.	Nil.
Body weight	2,390 gm.	2,270 gm.	Nil.	Nil.

CURVE 2.—GROUP 1, RABBIT

Bacilli Inoculated	Third Day	Eighteenth Day	[illegible]	[illegible]
B. typhosus	1,000 million	2,000 million	Nil.	Nil.
B. paratyphosus A	500 million	1,000 million	Nil.	Nil.
B. paratyphosus B	500 million	1,000 million	Nil.	Nil.
Body weight	2,050 gm.	1,990 gm.	[illegible]	[illegible]

CURVE 3.—GROUP 2, RABBIT 3

Bacilli Inoculated	Fourth Day	Fifteenth Day	Seventieth Day	Eightieth Day
B. typhosus	Nil.	Nil.	1,000 million	2,000 million
B. paratyphosus A	500 million	1,000 million	Nil.	Nil.
B. paratyphosus B	500 million	1,000 million	Nil.	Nil.
Body weight	2,040 gm.	2,250 gm.	2,340 gm.	2,480 gm.

CURVE 4.—GROUP 2, RABBIT 4

Bacilli Inoculated	Fourth Day	Fifteenth Day	Seventieth Day	Eightieth Day
B. typhosus	Nil.	Nil.	1,000 million	2,000 million
B. paratyphosus A	500 million	1,000 million	Nil.	Nil.
B. paratyphosus B	500 million	1,000 million	Nil.	Nil.
Body weight	1,480 gm.	1,510 gm.	1,610 gm.	1,640 gm.

Note: Rabbit 4 developed a "wry" neck through fighting on the seventy-eighth day.

CURVE 5.—GROUP 3, RABBIT 5

Bacilli Inoculated	Fourth Day	Fifteenth Day	Seventieth Day	Eightieth Day
B. typhosus	1,000 million	2,000 million	Nil.	Nil.
B. paratyphosus A	Nil.	Nil.	500 million	1,000 million
B. paratyphosus B	Nil.	Nil.	500 million	1,000 million
Body weight	2,060 gm.	2,230 gm.	2,000 gm.	2,220 gm.

Rabbit 5 developed a suppurating ear in the twenty-second day which continued throughout the experiment.

CURVE 6.—GROUP 3, RABBIT 6

Bacilli Inoculated	Fourth Day	Fifteenth Day	[illegible]	[illegible]
B. typhosus	1,000 million	2,000 million	Nil.	Nil.
B. paratyphosus A	Nil.	Nil.	Nil.	Nil.
B. paratyphosus B	Nil.	Nil.	Nil.	Nil.
Body weight	1,250 gm.	1,400 gm.	[illegible]	[illegible]

Rabbit 6 died on the twelfth day with a broken neck caused by fighting.

CURVE 7.—GROUP 4, RABBIT 7

Bacilli Inoculated	[illegible]	[illegible]	Second Day	Eleventh Day
B. typhosus	Nil.	Nil.	1,000 million	2,000 million
B. paratyphosus A	Nil.	Nil.	500 million	1,000 million
B. paratyphosus B	Nil.	Nil.	500 million	1,000 million
Body weight	[illegible]	[illegible]	1,290 gm.	1,400 gm.

CURVE 8.—GROUP 4, RABBIT 8

Bacilli Inoculated	[illegible]	[illegible]	Second Day	Eleventh Day
B. typhosus	Nil.	Nil.	1,000 million	2,000 million
B. paratyphosus A	Nil.	Nil.	500 million	1,000 million
B. paratyphosus B	Nil.	Nil.	500 million	1,000 million
Body weight	[illegible]	[illegible]	1,210 gm.	1,270 gm.

CURVE 9.—GROUP 5, RABBIT 9

Bacilli Inoculated	Ninth Day	[illegible]	[illegible]	[illegible]
B. typhosus	500 million	Nil.	Nil.	Nil.
B. paratyphosus A	250 million	Nil.	Nil.	Nil.
B. paratyphosus B	250 million	Nil.	Nil.	Nil.
Body weight	1,900 gm.	[illegible]	[illegible]	[illegible]

CURVE 10.—GROUP 5, RABBIT 10

Bacilli Inoculated	Ninth Day	[illegible]	[illegible]	[illegible]
B. typhosus	500 million	Nil.	Nil.	Nil.
B. paratyphosus A	250 million	Nil.	Nil.	Nil.
B. paratyphosus B	250 million	Nil.	Nil.	Nil.
Body weight	2,030 gm.	[illegible]	[illegible]	[illegible]

CURVE 11.—GROUP 6, W. G.

Bacilli Inoculated	Sixth Day	Fifteenth Day	[illegible]	[illegible]
B. typhosus	500 million	1,000 million	Nil.	Nil.
B. paratyphosus A	250 million	500 million	Nil.	Nil.
B. paratyphosus B	250 million	500 million	Nil.	Nil.

CURVE 12.—GROUP 6, J. G. J.

Bacilli Inoculated	Sixth Day	Twenty First Day	.....	.....
B. typhosus	500 million	1,000 million	Nil.	Nil.
B. paratyphosus A	250 million	500 million	Nil.	Nil.
B. paratyphosus B	250 million	500 million	Nil.	Nil.

CURVE 13.—GROUP 7, R. F. D. R.

Bacilli Inoculated	Third Day	Thirteenth Day	Thirty-Sixth Day	Forty-Fifth Day
B. typhosus	Nil.	Nil.	500 million	1,000 million
B. paratyphosus A	250 million	500 million	Nil.	Nil.
B. paratyphosus B	250 million	500 million	Nil.	Nil.

CURVE 14.—GROUP 7, H. W. T.

Bacilli Inoculated	Third Day	Thirteenth Day	Thirty-Eighth Day	Forty-Eighth Day
B. typhosus	Nil.	Nil.	500 million	1,000 million
B. paratyphosus A	250 million	500 million	Nil.	Nil.
B. paratyphosus B	250 million	500 million	Nil.	Nil.

CURVE 15.—GROUP 8, T. P.

Bacilli Inoculated	Third Day	Thirteenth Day	Thirty-Sixth Day	Forty-Fifth Day
B. typhosus	500 million	1,000 million	Nil.	Nil.
B. paratyphosus A	Nil.	Nil.	250 million	500 million
B. paratyphosus B	Nil.	Nil.	250 million	500 million

CURVE 16.—GROUP 8, E. A. W.

Bacilli Inoculated	Third Day	Thirteenth Day	Thirty-Eighth Day	Forty-Eighth Day
B. typhosus	500 million	1,000 million	Nil.	Nil.
B. paratyphosus A	Nil.	Nil.	250 million	500 million
B. paratyphosus B	Nil.	Nil.	250 million	500 million

CURVE 17.—GROUP 9, W. C. C.

Bacilli Inoculated	.....	.....	First Day	Twenty-First Day
B. typhosus	Nil.	Nil.	500 million	1,000 million
B. paratyphosus A	Nil.	Nil.	250 million	500 million
B. paratyphosus B	Nil.	Nil.	250 million	500 million

CURVE 18.—GROUP 9, F. H. M.

Bacilli Inoculated	.....	.....	First Day	Twenty-Second Day
B. typhosus	Nil.	Nil.	500 million	1,000 million
B. paratyphosus A	Nil.	Nil.	250 million	500 million
B. paratyphosus B	Nil.	Nil.	250 million	500 million

CURVE 19.—GROUP 10, J. W.

Bacilli Inoculated	Previous Typhoid Immunization	Ten Months Later	Nineteen Days Later
B. typhosus	(1) 500 million (2) 1,000 million	500 million	1,000 million
B. paratyphosus A	nil	250 million	500 million
B. paratyphosus B	nil	250 million	500 million

CURVE 20.—GROUP 10, E. H. N.

Bacilli Inoculated	Previous Typhoid Immunization	Thirty-Two Months Later	Forty Days Later
B. typhosus	(1) 500 million (2) 1,000 million (3) 1,000 million	500 million	1,000 million
B. paratyphosus A	nil	250 million	500 million
B. paratyphosus B	nil	250 million	500 million

CURVE 21.—GROUP 10, E. F. H.

Bacilli Inoculated	Previous Typhoid Immunization	Twenty-Two Months Later	Nine Days Later
B. typhosus	(1) 500 million (2) 1,000 million (3) 1,000 million	500 million	1,000 million
B. paratyphosus A	nil	250 million	500 million
B. paratyphosus B	nil	250 million	500 million

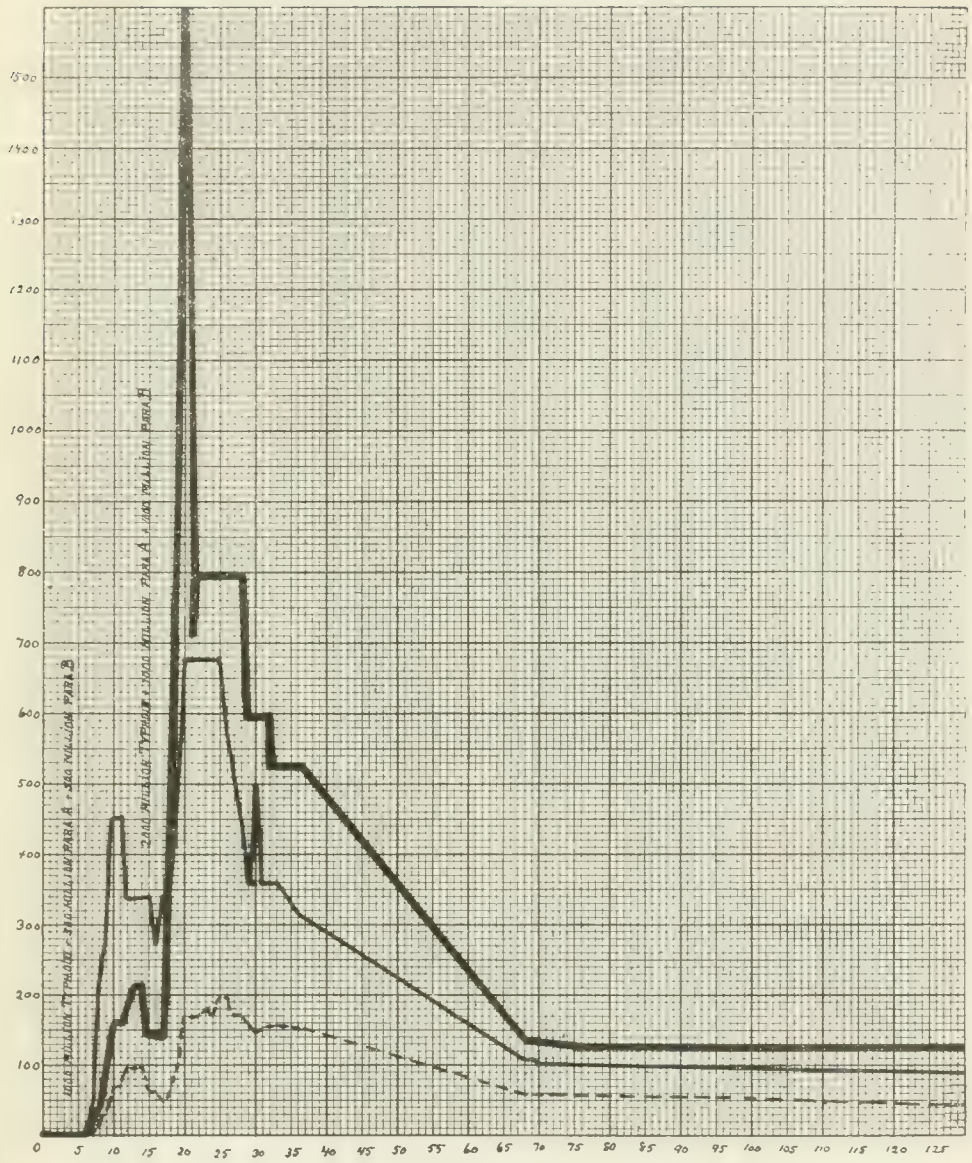
CURVE 22.—GROUP 11, A. D. G.

Bacilli Inoculated	Previous Typhoid Immunization	Fourteen Months Later	Sixteen Days Later
B. typhosus	(1) 1,000 million	500 million	1,000 million
B. paratyphosus A	nil	500 million	1,000 million
B. paratyphosus B	nil	500 million	1,000 million

The local and general reaction to this increased dose in curves 22 and 23 was not appreciably different from those following the more usual doses.

CURVE 23.—GROUP 11, W. C. D.

Bacilli Inoculated	Previous Typhoid Immunization	Twenty-Five Months Later	Eighteen Days Later
B. typhosus	(1) 500 million (2) 1,000 million (3) 1,000 million	500 million	1,000 million
B. paratyphosus A	nil.	500 million	1,000 million
B. paratyphosus B	nil.	500 million	1,000 million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0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125
1000 MILLION TYPHOID + 500 MILLION PARA A + 500 MILLION PARA B
2000 MILLION TYPHOID + 1000 MILLION PARA A + 1000 MILLION PARA B

Curve 1

TABLE 4.—Data from which Curve 1 Was Plotted

Day of Experiment	Weight of Rabbit, Gm.	Standard Agglutinin Units		
		B. typhosus	B. paratyphosus A	B. paratyphosus B
1	2,500	0	0	0
2	2,450	0	0	0
4	2,390	0	0	0
4	2,390	Inoculation,	1 c.c. T A B = 1,000 million typhoid, 500 million para A, 500 million para B	
5	2,350	0	0	0
6	2,350	0	2.70	0
7	2,350	26.59	50.67	6.87
8	2,310	44.32	202.70	27.77
9	2,250	88.63	270.27	37.03
10	2,200	159.57	450.43	69.44
11	2,200	159.57	450.43	69.44
12	2,260	186.17	337.83	97.0
13	2,240	212.76	337.83	97.0
14	2,200	212.76	337.83	97.0
15	2,270	141.70	337.83	64.0
15	2,270	Inoculation,	2 c.c. T A B = 2,000 million T, 1,000 million A, 1,000 million B	
16	2,180	141.70	270.27	62.0
17	2,200	141.70	331.83	48.0
18	2,200	354.59	337.83	62.0
19	2,120	709.14	506.75	97.0
20	2,200	1,595.74	675.68	169.0
21	2,270	709.14	675.68	169.0
22	2,190	797.87	675.68	169.0
23	2,340	797.87	675.68	180.0
24	2,190	797.87	675.68	169.0
25	2,200	797.87	675.68	193.0
26	2,150	797.87	563.06	193.0
27	2,300	797.87	506.75	169.0
28	2,200	797.87	450.43	169.0
29	2,260	595.23	357.14	159.0
30	2,390	595.23	500.17	145.0
31	2,270	595.23	357.14	152.0
32	2,220	529.1	357.14	151.0
33	2,250	259.1	357.14	159.0
36	2,280	529.1	314.28	151.1
68	2,570	134.0	107.85	36.5
69	2,490	134.0	107.14	32.64
74	2,470	129.0	100.0	50.0

TABLE 4.—Data from which Curve 1 Was Plotted—(*Continued*)

Day of Experiment	Weight of Rabbit, Gm.	Standard Agglutinin Units		
		B. typhosus	B. paratyphosus A	B. paratyphosus B
76	2,450	129.0	100.0	44.64
83	2,640	128.0	119.04	56.11
90	2,570	126.0	152.0	56.11
97	2,800	137.98	98.0	56.11
104	2,800	130.0	82.8	50.0
111	.....	120.0	82.8	35.6
118	2,760	104.0	82.8	35.6
125	2,810	112.0	122.0	28.0
132	2,710	120.0	115.0	28.0
139	2,630	130.0	122.0	32.0
146	.....	130.0	171.0	22.4
153	....	130.0	85.5	12.8
160	.....	130.0	85.5	28.0
167	.....	130.0	171.0	28.0

seen). On the next day (the third after the second inoculation, the fourteenth after the first) the new rise had commenced, for the titer was more than doubled and rapidly rose to a maximum on the fifth day (that is, the sixteenth day from the first inoculation). The next day reveals a fall of 50 per cent. The titer shows but little change from this point until the twenty-fourth day (from first inoculation), when it falls gradually until the thirty-second day (from first inoculation). When next examined after an interval of thirty-two days the agglutination titer had fallen 71 per cent. since the last examination (that is, the thirty-second day). Seventeen subsequent examinations covering a period of 139 days showed no further appreciable difference in agglutination titer, showing that it had reached a point that was practically equilibrium.[28]

The paratyphoid A agglutinins begin their rise on the second day (the first after inoculation), reaching the maximum of the first rise on the sixth day, after which there is a rapid fall (25 per cent.). The paratyphoid A curve shows no change until after the eleventh day. At this point the second inoculation is given. A negative phase (20 per cent.) occurs on the following day. From this point the new curve quickly rises (150 per cent.) reaching a maximum on the fifth day after the second inoculation (the sixteenth day after the first inoculation). No change in titer is seen from the fifth to eleventh day after the second inoculation. A rapid fall (50 per cent.) occurs from the eleventh to seventeenth day. From the seventeenth to twenty-first day (after the second inoculation) there is little change. When next examined after an interval of thirty-two days, it has fallen 66 per cent. As in the typhoid curve, the paratyphoid A has now reached its point of equilibrium.

The *paratyphoid B agglutinins* commence their rise on the third day, reaching a maximum on the sixth. This is followed by a rapid fall (33 per cent.) until the second inoculation on the eleventh day. The curve either continues

28. By the term equilibrium I refer to that condition in which the ratio between production and excretion of agglutinins is practically unity.

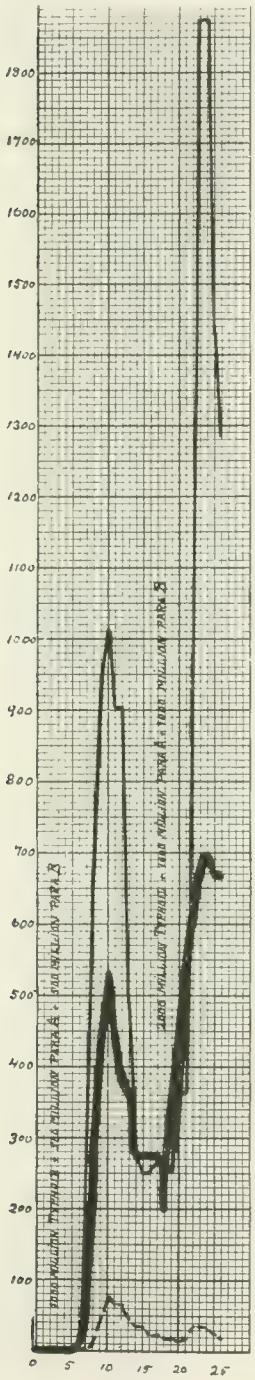
falling or a negative phase (20 per cent.) is exhibited for the next two days. The new rise commenced on the third day (the fourteenth from first inoculation) and reaches a maximum on the tenth day. The curve then behaves in a manner similar to that of the typhoid and paratyphoid A curves.[29]

Rabbit 2.—(Group 1, Curve 2.) *The typhoid agglutinins* commence their rise on the third day after inoculation, reaching the maximum on the seventh. A rapid fall (50 per cent.) follows for the next four days, after which the curve shows no change for three days, finally falling 33 per cent. on the

TABLE 5.—Data from which Curve 2 Was Plotted

Day of Experiment	Weight of Rabbit, Gm.	Standard Agglutinin Units		
		B. typhosus	B. paratyphosus A	B. paratyphosus B
1	....	0	0	0
2	.....	0	0	0
3	2,050	0	0	0
3	2.050	Inoculation, 1 c.c. T A B = {1,000 million typhoid, 500 million A, 500 million B}		
4	1,940	0	0	0
5	.....	0	0	0
6	2,050	4.25	13.51	0
7	1,970	53.18	100.00	0
8	2,050	265.95	675.68	16.9
9	1,970	443.25	945.94	48.0
10	1,920	531.90	1,013.51	72.2
11	2,060	443.25	900.89	64.0
12	1,920	398.93	900.89	64.0
13	1,940	365.69	506.75	48.0
14	.....	272.81	271.42	36.0
15	. ...	272.81	250.0	36.0
16	1,980	272.81	250.0	21.2
17	1,920	272.81	265.25	21.2
18	1,990	198.41	271.42	19.3
18	1,990	Inoculation, 2 c.c. T A B = {2,000 million T, 1,000 million A, 1,000 million B}		
19	1,895	306.63	250.0	19.3
20	1,890	277.71	357.14	17.4
21	1,960	529.1	357.14	19.3
22	1,950	595.23	1,071.42	32.0
23	1.900	661.37	1,857.42	32.0
24	1,910	694.44	1,857.42	32.0
25	1,980	661.37	1,428.57	24.0
26	.....	661 37	1,285.71	20.5

29. For the sake of brevity typhoid and *B. typhosus* will often be expressed as T; paratyphoid A and *B. paratyphosus A* as A, and paratyphoid B and *B. paratyphosus B* as B.


1900
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10
15
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25

Curve 2

fifteenth day. At this point the second inoculation was given. The curve starts its new rise the following day (no negative phase being seen), and reaches its maximum in six days (twenty-first from first inoculation), after which it falls for the next two days. No further examination was made.

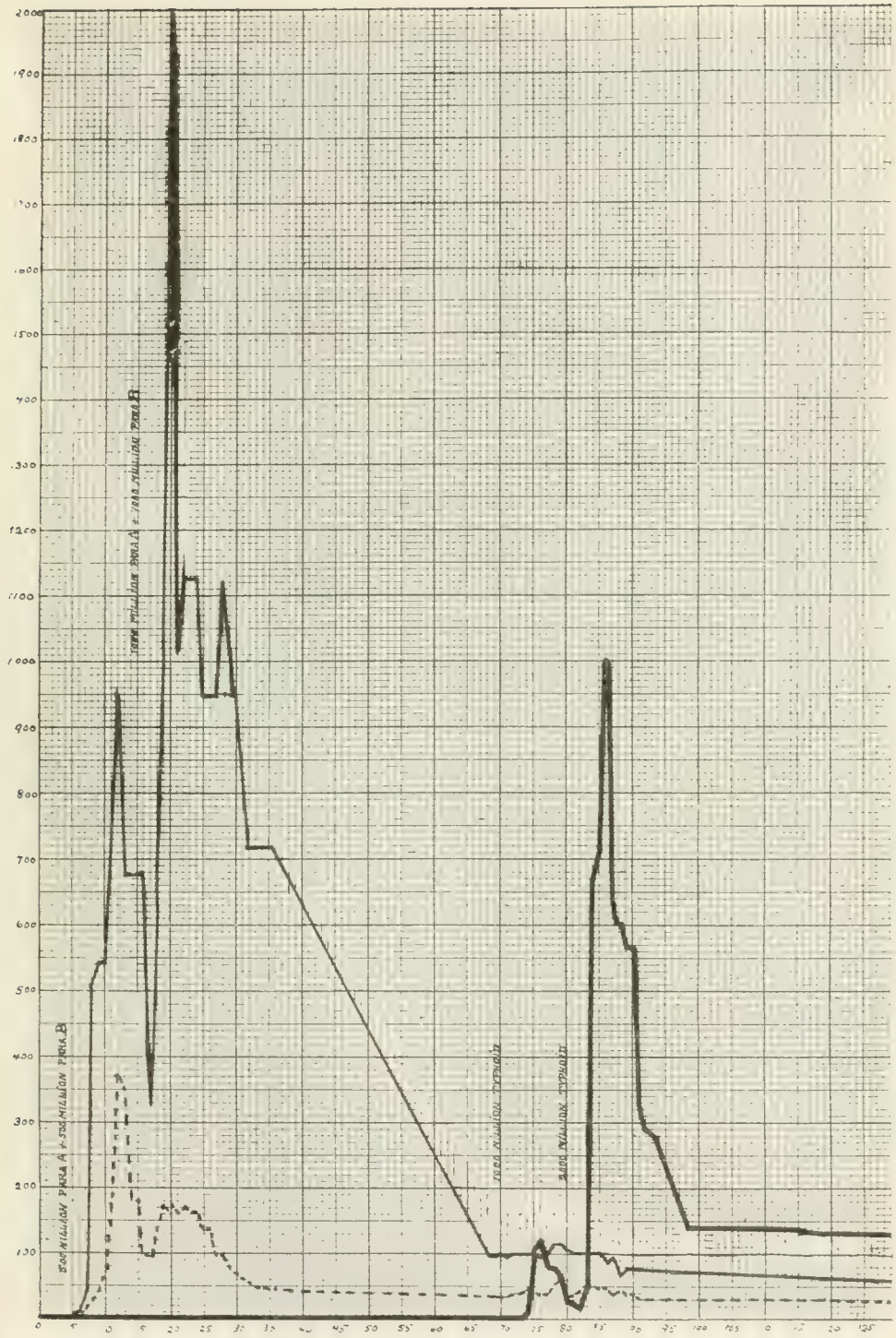
The paratyphoid A agglutinins commence their rise on the third day, reaching the maximum on the seventh. A rapid fall then follows for four days. The curve then shows no change for four. The second inoculation was given at this point (fifteenth day). *A negative phase* occurs on the following day. On the second day from this inoculation the curve quickly arises to a maximum (800 per cent.) on the fifth day (twentieth from first inoculation). The curve shows no change when examined on the next day. A rapid fall follows for the next two days. No further examinations were made.

The paratyphoid B curve commences on the fourth day after inoculation, reaching its maximum on the seventh day. The titer gradually falls for the next eight days. The second inoculation is given on the fifteenth day. The B titer shows no change on the next day. A small negative phase appears on the second day. The titer then rises to its maximum on the fourth day (nineteenth day from the first inoculation), shows no change for three days, and then rapidly falls for two days. No further examination was made.

Rabbit 3.—(Group 2, Curve 3.) *The T. agglutinins* are unaffected by the two doses of *A B* vaccine injected and the *T* titer did not rise above the base line. On the fourth day after the first *T* inoculation (fifty-ninth day after the second *A B* inoculation; seventieth day after the first *A B* inoculation) the *T* titer rose, reaching a maximum on the sixth day. It then fell for the next five days. At this point the second *T* inoculation was given. The titer showed no change the following day. A negative phase was seen on the second day. The curve began its new rise on the third day, reaching the maximum on the sixth day. The titer then falls for the next twelve days after which it appears to have reached its point of equilibrium.

The paratyphoid A curve commences its rise on the second day after inoculation, reaching its maximum on the eighth day. On the ninth day the titer falls rapidly (33 per cent.) and then shows no change until the eleventh day. At this point the second inoculation was given. The titer showed no change the following day. A negative phase (50 per cent.) appeared on the second day. On the third day the titer rises, reaching its maximum (700 per cent.) on the fifth day (from the second inoculation). The titer then falls rapidly (50 per cent.) and shows no change for ten days, and then falls gradually until the thirty-second day from the first inoculation. When examined after an interval of thirty-two days the titer has fallen 85 per cent. The first *T* inoculation is given two days later. A slight negative phase appears on the day following. A slight rapid rise then ensues on the second day. From this point the titer shows no change until the fifth day, when a fall commences, which continues until eighth day. On the eighth day the *A* titer rises. This corresponds with the maximum of the first rise in the *T* curve. On the tenth day the second *T* inoculation is given. This appears to have no appreciable effect on the *A* curve. On the eighth day after the second *T* inoculation there is a fall in titer (40 per cent.) after which the curve appears to have reached its equilibrium.

The paratyphoid B curve rises on the third day after inoculation, reaching its maximum on the eighth day. It then falls (10 per cent.) and shows no change until eleventh day. At this point the second inoculation is given. A negative phase (45 per cent.) is seen for the following two days. The second rise commences on the third day after the second inoculation, reaching its maximum on the fourth where it appears to remain for the next three days, after which it gradually falls (66 per cent.) until the twenty-first day (after the second *A B* inoculation). An interesting fact in the *B* Curves of both 2 and 3 is that the rise after the second *A B* inoculation is appreciably less



Curve 3

TABLE 6.—Data from which Curve 3 Was Plotted

Day of Experiment	Weight of Rabbit, Gm.	Standard Agglutinin Units		
		B. typhosus	B. paratyphosus A	B. paratyphosus B
1	2,670	0	0	0
2	2,600	0	0	0
4	2,640	0	0	0
4	2,640	Inoculation, 1 c.c. A B = 500 millio n para A + 500 millio n para B		
5	2,420	0	0	0
6	2,440	0	2.25	0
7	2,450	0	45.04	3.08
8	2,420	0	508.47	26.45
9	2,424	0	540.54	46.29
10	2,370	0	540.54	77.15
11	2,350	0	675.68	185.18
12	2,330	0	945.94	370.37
13	2,430	0	675.68	343.95
14	2,350	0	675.68	180.0
15	2,250	0	675.68	180.0
15	2,250	Inoculation, 1 c.c. A B = 1,000 milli on para A + 1,000 milli on para B		
16	2,210	0	675.68	96.0
17	2,350	0	337 83	96.0
18	2,350	0	675.68	137.8
19	2,200	0	1,013.51	169.0
20	2,400	0	2,027.02	169.0
21	2,320	0	1,013.51	160.0
22	2,360	0	1,126.12	169.0
23	2,410	0	1,126.12	160.0
24	2,330	0	1,126.12	160.0
25	2,320	0	945.94	137.0
26	2,310	0	945.94	137.0
27	2,300	0	945.94	96.0
28	2,270	0	1,122.41	96.0
29	2,380	0	1,020.37	75.0
30	2,470	0	952.38	67.5
31	2,310	0	952.38	60.0
32	2,300	0	714.28	55.0
33	2,350	0	714.28	48.0
36	2,320	0	714.28	48.0
68	2,710	0	95.0	32.0
69	2,720	0	95.23	32.64
70	2,540	0	100.0	32.64

TABLE 6.—Data from which Curve 3 Was Plotted—(*Continued*)

Day of Experiment	Weight of Rabbit, Gm.	Standard Agglutinin Units		
		B. typhosus	B. paratyphosus A	B. paratyphosus B
70	2,540	Inoculation, 1.0 c.c. = 1,000 million T		
71	2,570	0	95.23	32.64
72	2,560	0	100.0	35.71
73	2,430	0	100.0	35.71
74	2,500	3.15	100.0	44.64
75	2,500	120.0 – 246.0	99.11	44.64
76	2,510	126.0	95.23	35.71
77	2,660	79.0	95.23	35.71
78	2,580	79.0	112.24	53.57
79	2,420	67.0	112.24	56.11
80	2,480	32.2	107.14	35.71
80	2,480	Inoculation, 2 c.c. T = 2,000 millio n T		
81	2,300	32.2	100.0	35.71
82	2,490	29.0	100.0	50.0
83	2,480	59.5	100.0	50.0
84	2,500	670.0	100.0	50.0
85	2,520	720.0	100.0	50.0
86	2,420	1,000.0	88.59	50.0
87	2,335	630.0	99.11	35.71
88	2,410	600.0	62.50	44.64
89	2,500	561.0	71.42	32.14
90	2,380	561.0	71.42	32.64
91	2,680	590.0 – 322.0	59.52	30.35
92	2,510	290.0	64.28	30.35
93	2,500	280.0	64.28	30.35
94	2,220	255.0	56.11	30.35
96	2,500	280.0	64.28	30.35
98	2,630	137.98	54.0	30.35
100	2,600	137.98	54.0	30.35
102	2,900	137.98	59.0	30.35
104	2,730	137.98	59.0	30.35
106	2,720	137.98	82.7	30.35
108	2,720	137.98	51.5	30.35
112	2,760	137.98	59.0	30.35
116	2,740	137.98	42.0	30.35
120	2,980	130.0	42.0	30.35
125	2,880	130.0	51.5	25.5

TABLE 6.—Data from which Curve 3 Was Plotted—(*Continued*)

Day of Experiment	Weight of Rabbit, Gm.	Standard Agglutinin Units		
		B. typhosus	B. paratyphosus A	B. paratyphosus B
132	2,980	59.6	45.6	13.0
139	2,990	59.6	45.6	20.5
146	.....	54.0	28.6	9.5
153	.....	130.0	47.5	20.5
160	.....	138.0	47.5	23.6
167	.....	130.0	47.5	13.0

than the rise after the first inoculation, and unless one can suppose that a rapid rise and fall have occurred within twenty-four hours so that daily readings would not record it, it would appear that this forms an exception to the more general rule that the rise of agglutinins following the second inoculation is greater than that following the first.

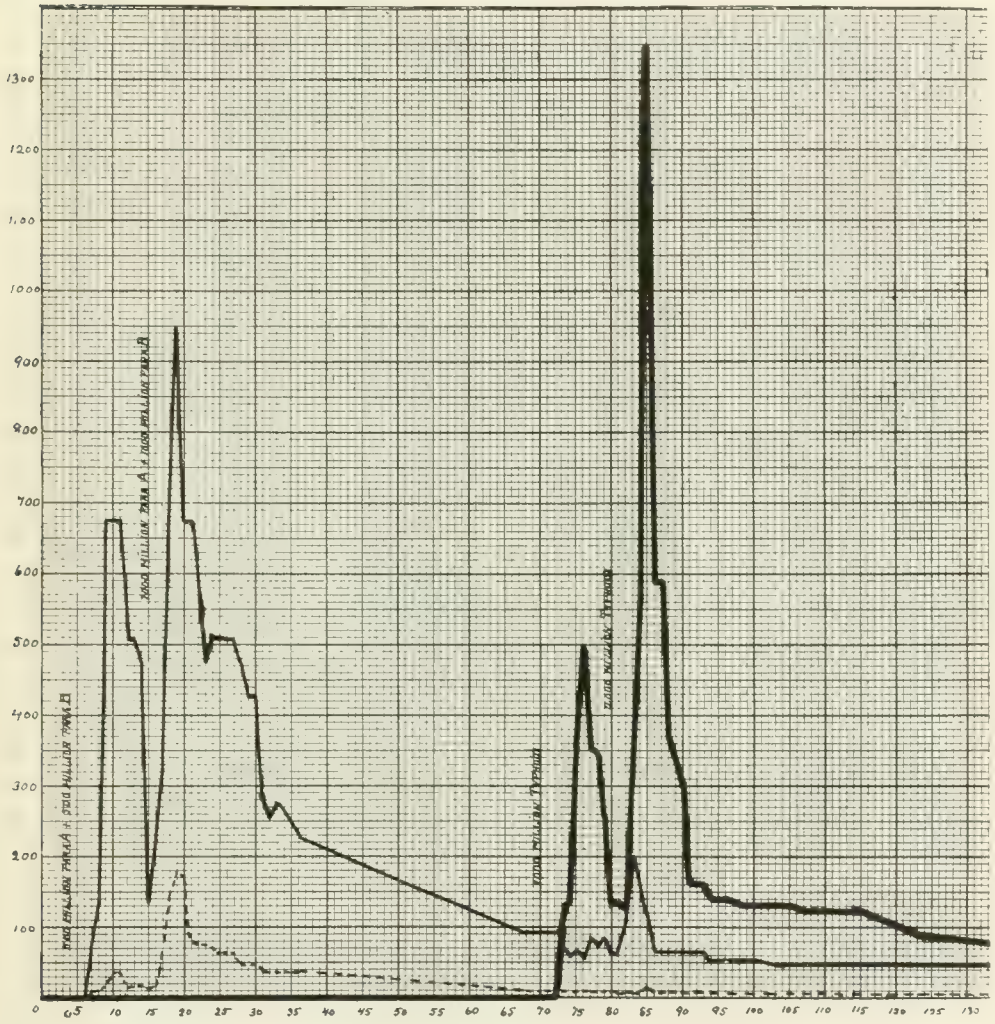
When next examined after an interval of thirty-two days the *B* titer has fallen 30 per cent. The *T* inoculation is given on the sixty-sixth day (after the first inoculation). No appreciable negative phase occurs. The rise of the *B* titer commences on the second day, reaching a maximum on the ninth, falling again on the tenth. At this point the second *T* inoculation is given. No negative phase occurs. A rise to a maximum is noticed on the second day. The curve then shows no further change until the fifth day, when it falls again, resuming its equilibrium on the ninth day (from the second typhoid inoculation; eighty-fifth day from first inoculation). The subsequent fall is very gradual.

Rabbit 4.—(Group 2, Curve 4.) *The typhoid agglutinins* were unaffected by the two doses of mixed *A* and *B* vaccine injected and the typhoid titer did not rise above the base line. On the third day after the first *T* inoculation (sixty-ninth day after the first *A B* inoculation; fifty-eighth day after the last *A B* inoculation), the *T* titer commenced to rise rapidly, reaching its maximum on the sixth day. A rapid fall then follows until the tenth day. At this point the second typhoid inoculation was given. The curve shows no change for the first day, but a negative phase appears on the second day. On the third day the rapid rise then commences, reaching its maximum (900 per cent.) on the fifth day. A rapid fall (30 per cent.) followed by a more gradual one then ensues and by the eleventh day after the last *T* inoculation (eighty-seventh from the first *A B* inoculation) the *T* titer had reached its point of equilibrium.

The paratyphoid A agglutinins commence their rise on the third day after inoculation, reaching their maximum on the fifth day. The titer shows no change for three days. A rapid fall (80 per cent.) then follows, until the eleventh day. At this point the second inoculation is given. No negative phase is seen and the titer rises on the first day, reaching its maximum (700 per cent.) on the fourth day (the fifteenth day after the first inoculation). The titer then falls rapidly (45 per cent.) for the next four days and then shows no change for another four days, after which the fall is again rapid (25 per cent.) until the twenty-first day after the second inoculation (thirty-second after the first).

When next examined after an interval of thirty-two days, the titer has dropped another 54 per cent. and is practically in equilibrium. The first *T* inoculation two days later (that is, fifty-five days after second *A B* inoculation and sixty-sixth day after first *A B* inoculation), causes the titer to rise on

the following day (no negative phase being seen), and a maximum is reached on the second day. The titer regains its point of equilibrium on the tenth day. At this point the second typhoid inoculation is given. The titer then rises on the second day (no negative phase appearing), and a maximum is reached on the third day. The succeeding fall is rapid and equilibrium is reached on the sixth day (eighty-second day after first *A B* inoculation). The subsequent fall in titer was but slight.



Curve 4

The paratyphoid B agglutinins commence their rise on the third day after the first inoculation, reaching their maximum on the sixth day. The titer shows very little change until the tenth day and falls slightly on the eleventh. At this point the second inoculation is given. The titer rises on the following day (no negative phase being seen). The maximum (300 per cent.) is reached

TABLE 7.—Data from which Curve 4 Was Plotted

Day of Experiment	Weight of Rabbit, Gm.	Standard Agglutinin Units		
		B. typhosus	B. paratyphosus A	B. paratyphosus B
1	.....	0	0	0
2	1,420	0	0	0
4	1,480	0	0	0
4	1,480	Inoculation, 1 c.c. A B = ½500 million para A ½500 million para B		
5	1,520	0	0	0
6	1,530	0	0	0
7	1,540	0	67.56	3.08
8	1,560	0	135.13	7.40
9	1,557	0	675.67	18.51
10	1,510	0	675.68	37.03
11	1,490	0	675.68	37.03
12	1,580	0	472.07	18.0
13	1,510	0	506.75	18.0
14	1,450	0	472.97	18.0
15	1,510	0	135.13	13.0
15	1,510	Inoculation, 2 c.c. A B = ½1,000 million para A ½1,000 million para B		
16	1,550	0	236.48	14.0
17	1,550	0	337.83	64.0
18	1,560	0	675.68	145.0
19	1,500	0	945.94	180.0
20	1,540	0	675.68	170.0
21	1,560	0	675.68	80.0
22	1,530	0	506.75	72.0
23	1,560	0	472.97	72.0
24	1,520	0	563.06	69.0
25	1,550	0	506.75	62.0
26	1,580	0	506.75	64.0
27	1,590	0	506.75	62.0
28	1,550	0	472.97	48.0
29	1,700	0	428.57	48.0
30	1,720	0	428.57	48.0
31	1,640	0	285.71	36.0
32	1,620	0	250.0	38.0
33	1,610	0	271.42	38.0
36	1,590	0	228.57	38.0
68	1,510	0	95.23	7.14

TABLE 7.—Data from which Curve 4 Was Plotted— *Continued.*

Day of Experiment	Weight of Rabbit, Gm.	Standard Agglutinin Units		
		B. typhosus	B. paratyphosus A	B. paratyphosus B
69	1,580	0	95.23	7.14
70	1,600	0	71.42	7.14
70	1,600	Inoculation, 1 c.c. T = 1,000 million typhoid		
71	1,510	0	95.23	7.14
72	1,520	0	95.23	7.14
73	1,510	100.0	71.42	7.14
74	1,560	136.0	59.52	7.14
75	1,590	352.0	64.28	2.85 - 7.14
76	1,569	500.0	57.14	5.71
77	1,620	352.0	85.71	6.28
78	1,610	340.0	71.42	6.28
79	1,570	255.0	85.71	6.28
80	1,640	133.0	59.52	5.17
80	1,640	Inoculation, 2 c.c. T = 2,000 million T		
81	1,530	133.0	59.52	2.85
82	1,450	126.0	59.52 - 107.14	5.30
83	1,440	320.0	59.52 - 142.84 196.42	5.30
84	1,470	561.0	59.52 - 96.93	5.30
85	1,420	1,340.0	119.04	10.71
86	1,410	590.0 – 340.0	64.28	5.71
87	1,490	590.0 – 340.0	64.28	2.57
88	1,480	590.0 – 567.0	72.77	2.85
89	1,500	297.0 – 516.0	64.28	2.57
90	1,460	297.0	64.28	2.37
91	1,620	160.0	71.42	4.57
92	1,560	160.0	64.28	4.57
93	1,540	160.0	64.28	5.71
94	1,530	140.0	53.57	5.42
96	1,580	140.0	47.14	5.0
98	1,610	137.98	46.5	5.0
100	1,680	137.98	46 5	5.71
102	1,870	137.98	49.0	4.27
104	1,770	137.98	44.2	4.0
106	1,780	137.98	44.2	4.0
108	1,740	129.0	44 2	3.96
112	1,780	125.7	35.6	4.37

TABLE 7.—Data from which Curve 4 Was Plotted—(*Continued*)

Day of Experiment	Weight of Rabbit, Gm.	Standard Agglutinin Units		
		B. typhosus	B. paratyphosus A	B. paratyphosus B
116	1,840	125.7	35.6	4.37
120	1,940	103.9	42.5	5.71
125	2,030	87.5	51.5	2.3
132	2,060	60.0	45.0	1.28
139	2,160	59.4	40.0	1.92
146	.....	65.0	50.0	2.55
153	.....	65.0	50.0	1.92
160	.....	52.0	47.5	1.92
167	.....	43.0	43.0	1.02

on the fourth day. A rapid fall (56 per cent.) follows until the seventh day. From this point until the sixteenth day the fall is more gradual (25 per cent.). There is but slight change in titer from the sixteenth to nineteenth day after the second inoculation (twenty-seventh to thirtieth day after the first inoculation). When examined again after an interval of thirty-two days (sixty-fourth day after the first *A B* inoculation) the titer dropped another 80 per cent. and had reached a point of equilibrium. The first *T* inoculation two days later (fifty-fifth day after the last *A B* inoculation; sixty-sixth day after the first *A B* inoculation) had no appreciable effect on the *B* titer. The second *T* inoculation was given ten days later. A negative phase occurred on the following day and the titer rose on the second day, reaching a maximum on the fifth day, falling again to its point of equilibrium on the seventh day.

Rabbit 5.—(Group 3, Curve 5.) *The typhoid agglutinins* commenced their rise on the third day after inoculation, attaining their maximum on the eleventh day. At this point the second *T* inoculation was given. The titer showed no change for the next three days (no negative phase being seen). On the fourth day after the last inoculation (the fifteenth after the first) the titer rose rapidly, reaching its maximum (100 per cent.) the same day. The curve shows no change for the next two days and then rapidly falls (25 per cent.) on the seventh and eighth days. The titer shows no change for the next four days and then gradually falls another 25 per cent. until the sixteenth day (twenty-seventh from the first inoculation). The titer from the sixteenth to twenty-first day shows no change. When next examined after an interval of thirty-two days a further fall (37 per cent.) has taken place and the curve has evidently reached its point of equilibrium. The first inoculation of *A B* vaccine two days later (that is, fifty-fifth day from the last *T* inoculation and sixty-sixth from the first) has no effect on the *T* titer, but the second *A B* inoculation ten days later causes the titer to rise on the fifth day (no negative phase being seen). The maximum is reached on the eighth day. On the eleventh day (eighty-eighth day after the first *T* inoculation) the curve has resumed its point of equilibrium and the subsequent fall is but gradual.

The paratyphoid A agglutinins show a slight rise on the fifth day after the first *T* inoculation, which reaches its maximum on the eleventh day. At this point the second *T* inoculation is given. The only effect produced on the *A* titer is that it does not show the natural fall, no change from the maximum produced by the first inoculation being noted until the nineteenth day after the last inoculation (that is, thirtieth day after the first inoculation). When

TABLE 8.—Data from which Curve 5 Was Plotted

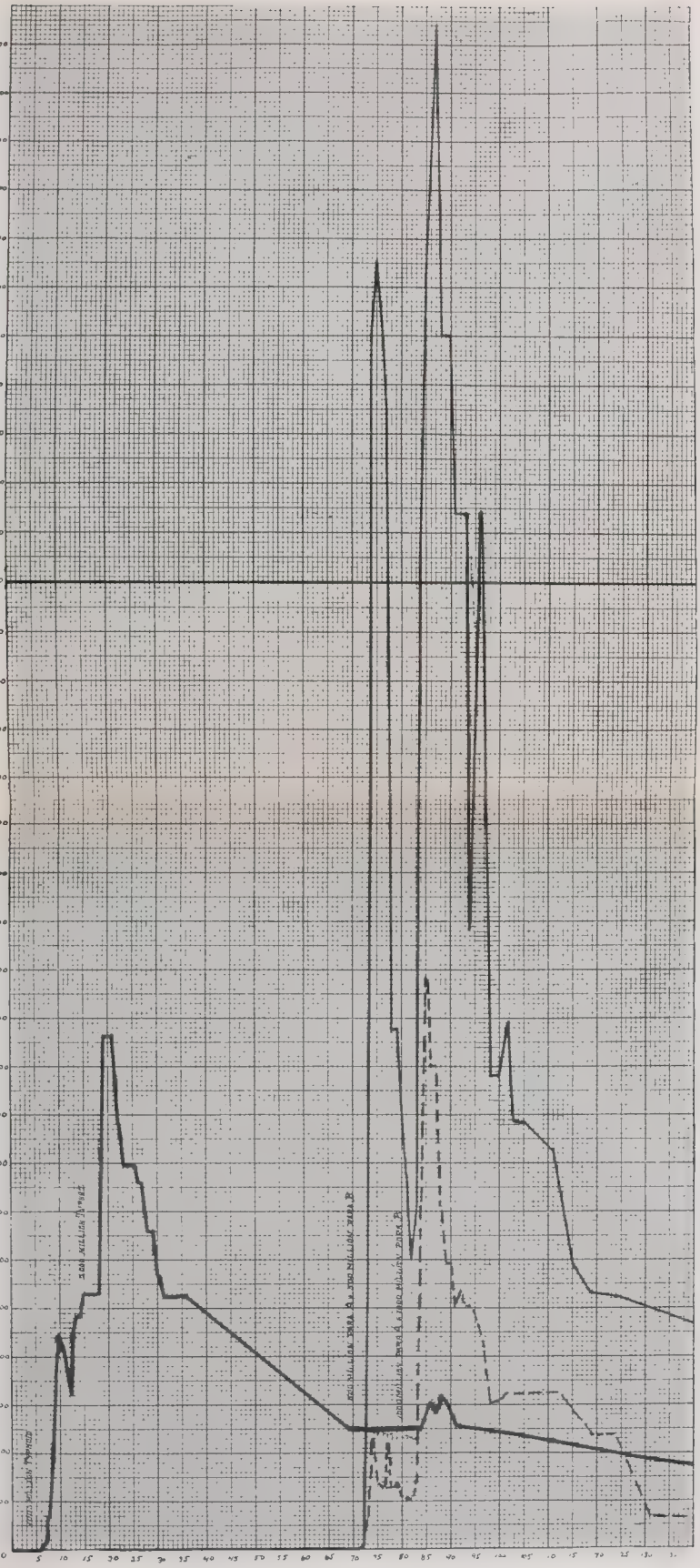
Day of Experiment	Weight of Rabbit, Gm.	Standard Agglutinin Units		
		B. typhosus	B. paratyphosus A	B. paratyphosus B
1	2,170	0	0	0
2	2,170	0	0	0
4	2,060	0	0	0
4	2,060	Inoculation, 1 c.c. T = 1,000 million typhoid		
5	2,000	0	0	0
6	2,060	1.59	0	0
7	2,140	21.27	0	0
8	2,140	197.53	0	0
9	2,120	354 59	0	1.18
10	2,060	443.25	0	0.78
11	2,060	417.87	0	0
12	2,080	319.14	0	0
13	2,140	443 25	1.01	0
14	2,070	478.72	1.01	0
15	2,230	531 91	2.7	0.78
15	2,230	Inoculation, 2 c.c. T = 2,000 million typhoid		
16	2,050	531.91	2.7	1.52
17	2,030	531.91	2.7	0.96
18	2,040	531.91	0	0.96
19	1,950	1,063.82	0	0.96
20	2,050	930.85	0	0.96
21	2,110	1,063.82	0	1.70
22	2,170	886 38	0	0.56
23	2,180	797.87	0	1.92
24	2,100	797.87	0	1.56
25	2,140	797.87	0	1.52
26	2,060	759.85	0	1.48
27	2,070	759.85	0	1.48
28	2,200	661.37	0	1.48
29	2,100	661.37	0	0.96
30	2,220	566.89	0	0
31	2,130	529.1	0	0
32	2,090	396.82	0	0
33	2,030	529.1	0	0
36	2,070	529.1	0	0
68	2,080	256.0	0	0
69	2,020	256.0	0	0
70	2,000	256.0	0	0

TABLE 8.—Data from which Curve 5 Was Plotted—(*Continued*)

Day of Experiment	Weight of Rabbit, Gm.	Standard Agglutinin Units		
		B. typhosus	B. paratyphosus A	B. paratyphosus B
70	2,000	Inoculation, 1 c.c. A B = 500 millio n A + 500 millio n B		
71	2,170	256.0	0	0
72	2,170	256.0	7 14	0
73	2,080	256.0	612.14	61.21
74	2,140	256.0	2,500.0	128.57
75	2,120	256.0	2,652.0	142.85
76	2,060	256.0	2,500.0	128.57
77	2,160	256.0	2,346.57	236.68
78	2,150	256.0	1.071.2	128.57
79	2,220	256.0	1,071.42	142.85
80	2,220	256.0	1,160.71 - 663.26	107.14
80	2,220	Inoculation, 2 c.c. A B = 1,000 mill. on A + 1,000 mill on B		
81	2,270	256.0	969.38 - 561.14	107.14
82	2,270	256.0	595.23	107.14
83	2,280	256.0	714.28	142.85
84	2,210	256.0	2,040.57	714.28
85	2,300	280.0	2,625.29	1,190.4
86	2,320	305.0	2,500.0	1,000.0
87	2,280	280.0	3,142.85	1,000.0
88	2,320	320.0	2,500.0	714.28
89	2,220	305.0	2,500.0	595.23
90	2,210	280.0	2,500.0	595.23
91	2,410	256.0	2,142.85	500.0
92	2,280	256.0	2,142.85	535.71
93	2,240	256.0	2,142.85	500.0
94	2,520	256.0	1,285.71	500.0
96	2,280	256.0	2,142.85	446.42
98	2,410	243.5	982.0	303.57
100	2,350	243.5	982.0	303.57
102	2,450	433.0	1,090.0	326.0
104	2,380	271.0	885.0	326.0
106	2,370	282.0	885.0	326.0
108	2,350	271.0	885.0	326.0
112	2,330	243.5	825.0	326.0
116	2,880	162.0	590.0	285.0
120	2,600	148.0	530.0	228.0
125	2,620	148.0	522.0	228.0
132	2,510	121.0	285.0	64.8

rabbit in the same cage, brought an end to the experiment at this point.

The *A* and *B* agglutinins were unaffected by the injections of *T* vaccine and their titer did not rise above the base line here.



Curve 5

TABLE 8.—Data from which Curve 5 Was Plotted—(Continued)

Day of Experiment	Weight of Rabbit, Gm.	Standard Agglutinin Units		
		B. typhosus	B. paratyphosus A	B. paratyphosus B
139	2,580	243.0	530.0	230.0
146	.....	148.5	450.0	64.0
153	.....	138.0	430.0	64.0
160	.....	114.0	400.0	64.0
167	.....	104.0	400.0	59.2

next examined after an interval of thirty-two days the titer has regained the base line of normal agglutination. The first *A B* inoculation is given two days later; that is, on the fifty-third day after the last *T* inoculation (sixty-sixth day after first *T* inoculation). The *A* curve commences its rise on the second day, reaching its maximum on the fifth day. The titer then shows no change for the next two days. A rapid fall (72 per cent.) ensues from the third to tenth day. At this point the second *A B* inoculation is given. A negative phase (6 per cent.) is seen for the next two days and the rise of titer commences on the third day, reaching its maximum (475 per cent.) on the seventh day after the last inoculation. The titer then falls 16 per cent. on the next day and then shows no change for the next three days. By the eleventh day a rapid fall (31 per cent.) occurs. From this point the curve is evidently in equilibrium, as the fall is but gradual.

The paratyphoid B agglutinins commence their small rise four days after the first *T* inoculation, reaching their maximum on the next day (fifth). A small fall (33 per cent.) occurs on the sixth day. From this point until the eleventh day the titer appears to remain a small distance above the base line of normal agglutination. The second inoculation is given on the eleventh day and the titer commences to rise on the following day (no negative phase being seen), and reaches its maximum (150 per cent.) on the eighth day. The titer then falls gradually until the fourteenth day (from second *T* inoculation; twenty-fifth day from the first inoculation). From this point until the twenty-seventh day (after the last inoculation) and after an interval of thirty-two days the titer had not risen above the base line of normal agglutination. The first *A B* inoculation is given two days later (that is, fifty-fifth day after the last *T* inoculation and sixty-sixth day after the first). The *B* agglutinins commence their rise on the third day following, reaching the maximum on the fourth day. A sharp fall (40 per cent.) is shown the next day, after which a more gradual fall (a further 14 per cent.) takes place until the tenth day. At this point the second *A B* inoculation is given. The titer rises on the third day, reaching a maximum (1,000 per cent.) on the fifth day. A rapid fall (60 per cent.) follows from the fifth to eleventh day. From this point the curve shows no change for four days, and then falls until the sixteenth day. From this point until the eighty-seventh day (after the last inoculation) the fall is but gradual.

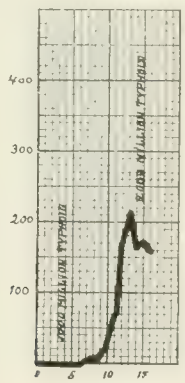
Rabbit 6.—(Group 3, Curve 6.) The typhoid agglutinins commenced their rise on the third day after the first inoculation, reaching the maximum on the ninth day. The titer fell (20 per cent.) on the tenth day and shows no change on the eleventh day. The second inoculation was given at this point. A negative phase occurred on the next day.

The death of Rabbit 6 from a broken neck, due to fighting with another rabbit in the same cage, brought an end to the experiment at this point.

The *A* and *B* agglutinins were unaffected by the injections of *T* vaccine and their titer did not rise above the base line here.

TABLE 9.—Data from which Curve 6 Was Plotted

Day of Experiment	Weight of Rabbit, Gm.	Standard Agglutinin Units		
		B. typhosus	B. paratyphosus A	B. paratyphosus B
1	1,280	0	0	0
2	1,240	0	0	0
4	1,250	0	0	0
4	1,250	Inoculation, 1 c.c. T = 1,000 million typhoid		
5	1,250	0	0	0
6	1,300	0	0	0
7	1,350	1.41	0	0
8	1,410	3.19	0	0
9	1,440	8.86	0	0
10	1,360	26.59	0	0
11	1,350	70.91	0	0
12	1,580	159.59	0	0
13	1,350	212.76	0	0
14	1,260	159.57	0	0
15	1,400	170.21	0	0
15	1,400	Inoculation, 2 c.c. T = 2,000 million typhoid		
16	1,310	159.57	0	0



Curve 6

Rabbit 7.—(Group 7, Curve 7.) *The typhoid agglutinins* commenced their rise on the third day after the first triple inoculation. The titer then rose rapidly until the ninth day, when the second inoculation was given. The curve continues its rapid rise to an apex on the twelfth day after the first triple inoculations (third day after the second triple inoculation). No negative phase, nor any break in the continuity of the curve (that is, no fall or plateau) was seen, until the fourth day (after the second inoculation) when a fall of 11 per cent. was noted.

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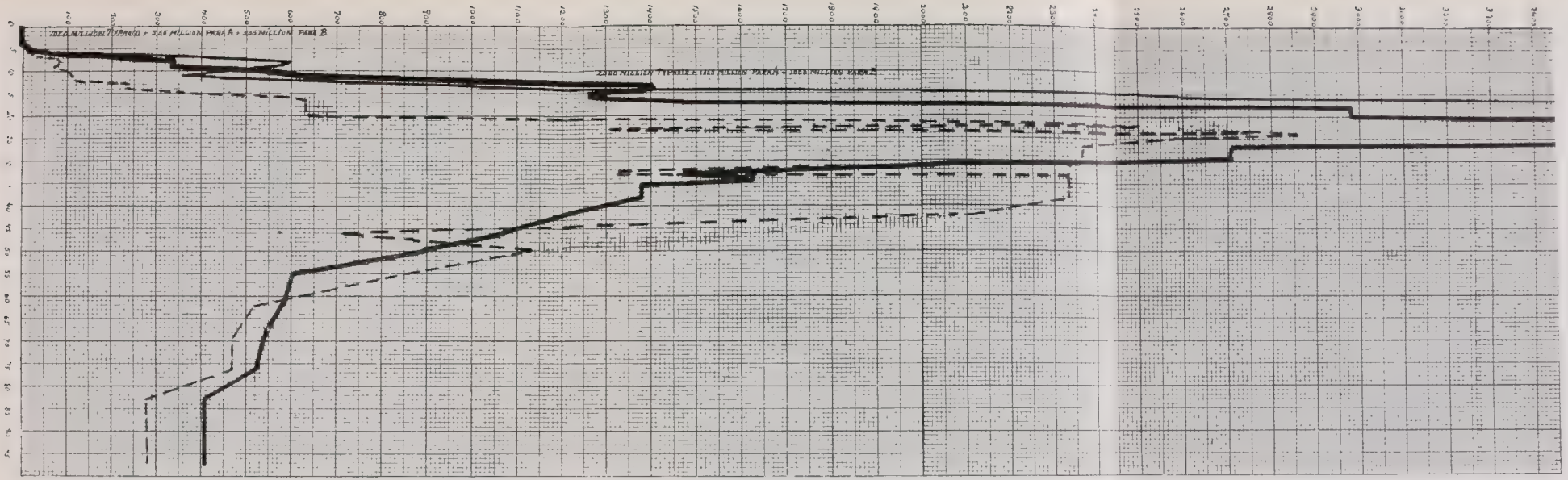
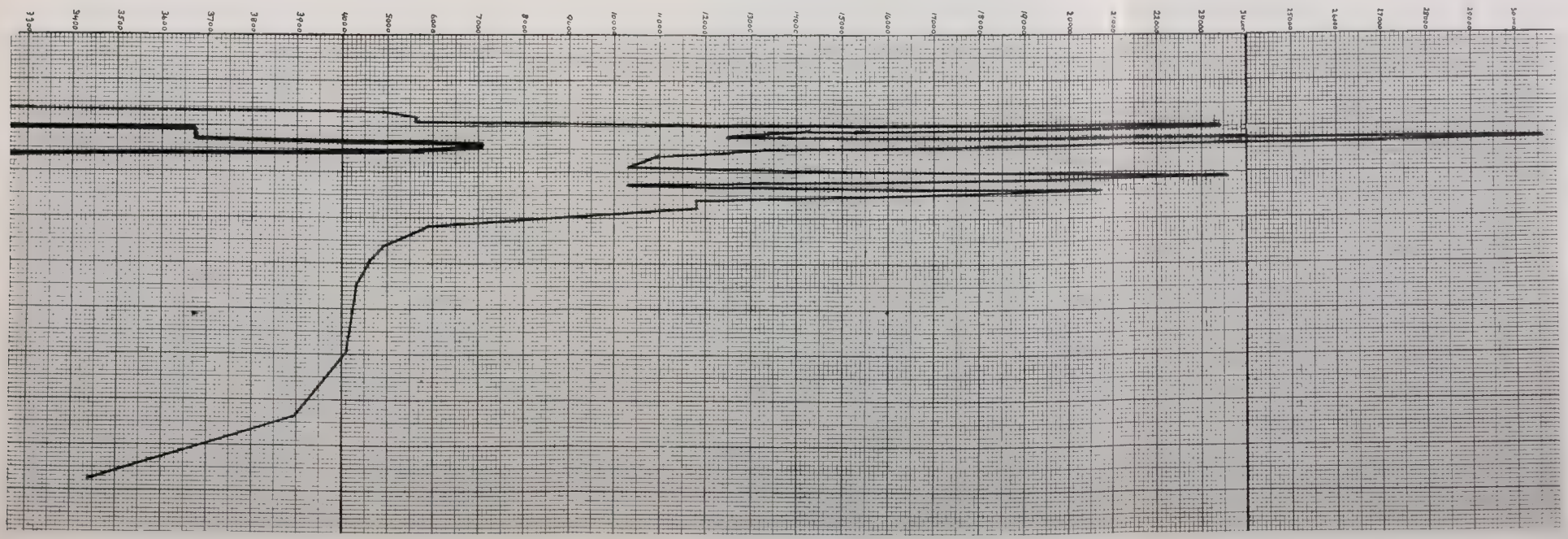


Curve 7—Part One



Curve 7—Part Two

TABLE 10.—Data from which Curve 7 Was Plotted

Day of Experiment	Weight of Rabbit, Gm.	Standard Agglutinin Units		
		B. typhosus	B. paratyphosus A	B. paratyphosus B
1	1,360	0	0	0
2	1,290	0	0	0
2	1,290	Inoculation, 1 c.c. T A B =	1,000 million T 500 million A 500 million B	
3	1,270	0	0	0
4	1,320	0	2.2	0
5	1,330	14.4	35.71	7.7
6	1,320	64.5	119.04	21.42
7	1,300	240.0	357.14	71.42
8	1,420	340.0	595.23	85.71
9	1,410	340.0	561.14	71.42
10	1,400	562.0	491.7	98.21
11	1,400	620.0	357.14	112.24
11	1,400	Inoculation, 2 c.c. T A B =	2,000 million T 2,000 million A 1,000 million B	
12	1,330	805.0	564.28	119.04
13	1,440	1,260.0	48.85	236.68
14	1,390	1,405.0	1,160.71	236.68
15	1,370	1,260.0	2,500.0	357.14
16	1,420	1,305.0	2,652.57	95.23
17	1,390	1,470.0	4,910.71	714.85
18	1,350	2,982.0	5,611.42	857.14
19	1,410	2,982.0	5,611.42	969.3 - 627.14
20	1,470	2,982.0	13,405.71	642.87
21	1,360	3,672.63	14,285.71	1,142.85 - 1,285.71
22	1,460	3,672.0	12,500.0	2,500.0
23	1,430	3,672.0	30,357.14	1,309.51
24	1,410	7,061.25	211,428.57 71,428.57 214,285.71	
25	1,450	5,625.0	13,264.57	2,597.40
27	1,470	2,711.04	10,944.0	2,366.85
29	1,530	2,705.58	10,318.0	2,366.85
31	1,510	2,029.22	28,584.0	2,232.14
33	1,650	1,483.89	10,318.0	1,326.45
35	1,560	1,623.87	20,696.0	2,232.14
37	1,570	1,379.87	11,792.0	2,232.14
39	1,590	1,379.87	11,792.0	2,232.14
43	1,630	1,205.71	17,856.0	2,105.26
47	1,730	1,066.62	4,316.0	714.28
51	1,830	892.0	4,632.0	1,122.0

TABLE 10.—Data from which Curve 7 Was Plotted—(*Continued*)

Day of Experiment	Weight of Rabbit, Gm.	Standard Agglutinin Units		
		B. typhosus	B. paratyphosus A	B. paratyphosus B
56	1,890	603.0	4,850.0	850.0
63	1,910	578.0	4,750.0	520.0
70	1,900	541.0	4,190.0	466.0
77	.....	520.0	4,500.0	477.0
84	.....	405.0	3,900.0	280.0
91	.....	520.0	4,500.0	291.0
98	.....	405.0	3,440.0	280.0

On the fifth day (after the second inoculation) the titer resumes its rise, reaching a maximum on the thirteenth day. The titer then falls rapidly (70 per cent.) from this point until the forty-fourth day. The *T* titer is then evidently in equilibrium for the fall from this point is but gradual.

The apex and subsequent fall of the curve noted, respectively, on the twelfth and thirteenth days after the first inoculation (third and fourth days after the second) might well represent the maximum of the rise due to the first inoculation and the negative phase following the second inoculation, even though this apex occurs after the second inoculation. For, as I shall point out later in the men's curves, if the second inoculation is given before the maximum of the rise due to the first inoculation is attained, a continuation of this rise to an apex and a subsequent fall may occur after the second inoculation, which suggests the maximum of the rise due to the first inoculation and the negative phase following the second inoculation. After this fall the titer resumes its rise, and the maximum due to the second inoculation is attained later. As the inoculations were given at a shorter interval (that is, nine days) in this experiment than in the others in the rabbits, it may explain this rise and fall which precedes the maximum of the second inoculation.

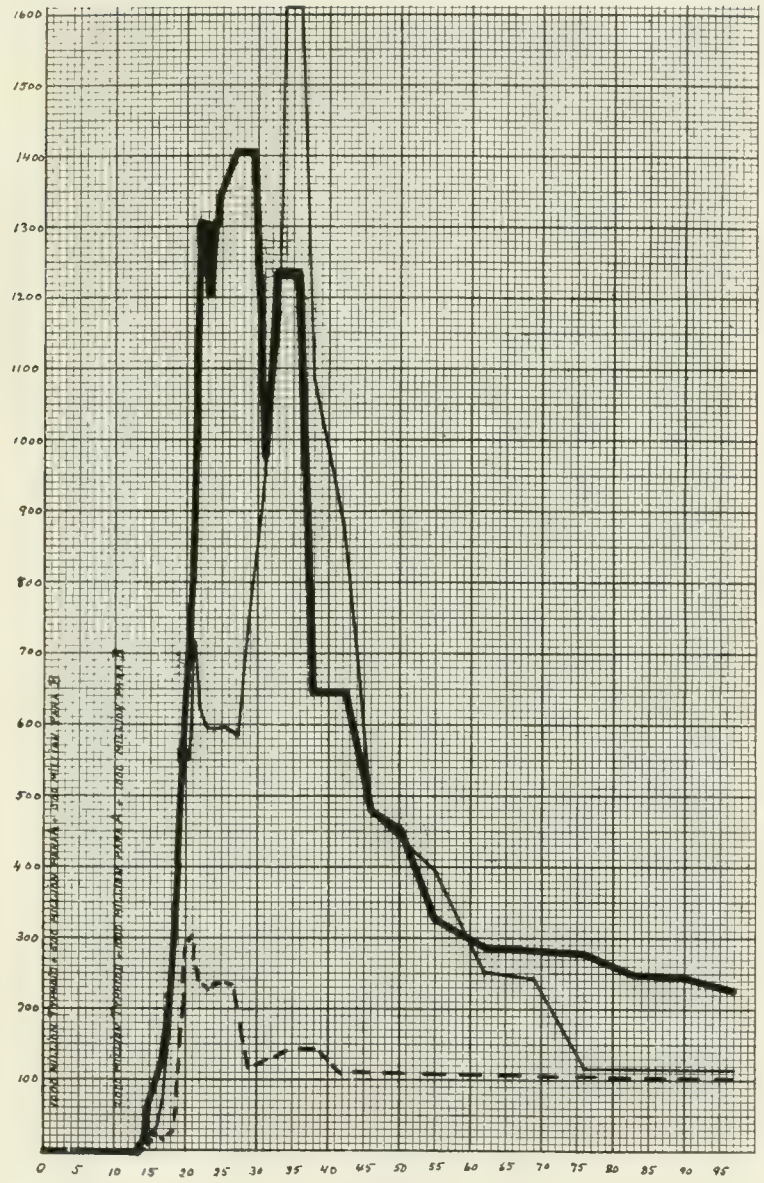
The paratyphoid A agglutinins commenced their rise on the second day after the first inoculation, reaching their maximum on the sixth day. A rapid fall (40 per cent.) then takes place until the ninth day. At this point the second inoculation takes place and the titer rises rapidly on the next day (no negative phase being seen).

The maximum of this second rise occurs on the ninth day (650 per cent.) or the twelfth day (750 per cent.) after the second inoculation.

The titer then falls until the thirty-sixth day (after the second inoculation). From this point the fall is but gradual and the curve appears to be in equilibrium.

The paratyphoid B agglutinins commence their rise in the third day. The titer then rises until the ninth day. At this point the second inoculation is given and the titer continues its rise (no negative phase being seen) and the maximum is reached on the thirteenth after the second inoculation. A rapid fall of titer (25 per cent.) then takes place on the fourteenth to twenty-first day after the second inoculation. From this point the titer shows no change for the next eight days and then another rapid fall (another 50 per cent.) occurs until the thirty-sixth day. At this point the curve appears to have reached its point of equilibrium for the subsequent fall is but gradual.

Rabbit 8.—(Group 4, Curve 8.) As the first inoculation produced absolutely no rise in agglutinative titer, the curves can best be interpreted by assuming that the first dose instead of being injected into the peritoneal cavity was, as is known to happen occasionally, injected directly into the bowel and the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Curve 8

TABLE 11.—Data from which Curve 8 Was Plotted

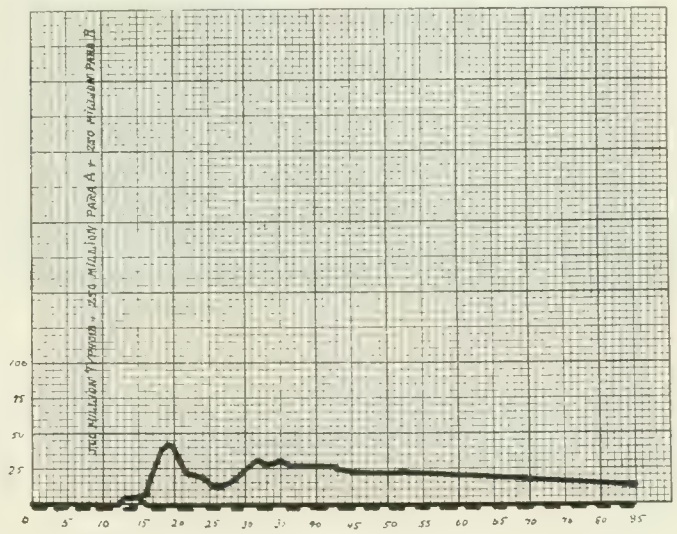
Day of Experiment	Weight of Rabbit, Gm.	Standard Agglutinin Units		
		B. typhosus	B. paratyphosus A	B. paratyphosus B
1	1,290	0	0	0
2	1,210	0	0	0
2	1,210	Inoculation, 1 c.c. T A B = 1,000 million T, 500 million A, 500 million B		
3	1,280	0	0	0
4	1,260	0	0	0
5	1,240	0	0	0
6	1,310	0	0	0
7	1,250	0	0	0
8	1,300	0	0	0
9	1,250	0	0	0
10	1,260	0	0	0
11	1,270	0	0	0
11	1,270	Inoculation, 2 c.c. T A B = 2,000 million T, 1,000 million A, 1,000 million B		
12	1,220	0	0	0
13	1,300	0	0	0
14	1,350	11.9	4.76	2.85
15	1,350	56.25	22.44	14.28
16	1,270	100.0	32.64	23.66
17	1,320	126.0	85.71	11.90
18	1,210	220.0	234.65	28.57
19	1,260	400.0	561.14	125.0
20	1,360	630.0	551.94	285.71
21	1,300	805.0	714.28	303.57
22	1,390	1,306.0	625.0	236.68
23	1,350	1,200.0	595.23	228.57
24	1,380	1,306.0	595.23	236.68
25	1,450	1,340.0	595.23	236.68
27	1,420	1,400.0	586.73	236.68
29	1,450	1,405.0	739.0	119.04
31	1,490	974.02	960.0	125.0
33	1,630	1,233.76	1,180.0	132.64
35	1,570	1,233.76	1,610.0	142.85
37	1,570	1,233.76	1,610.0	142.85
39	1,520	649.35	1,082.0	142.85
43	1,480	649.35	885.0	107.14
47	1,570	482.35	490.0	107.14
51	1,720	455.0	442.0	119.0
56	1,580	325.0	400.0	57.0

TABLE 11.—Data from which Curve 8 Was Plotted—(*Continued*)

Day of Experiment	Weight of Rabbit, Gm.	Standard Agglutinin Units		
		B. typhosus	B. paratyphosus A	B. paratyphosus B
63	1,260	284.0	251.0	106.0
70	1,828	325.0	243.0	119.0
77	.....	270.0	114.0	111.0
84	.....	243.0	114.0	111.0
91	.....	243.0	114.0	115.0
98	.....	227.0	114.0	128.0

vaccine voided without any absorption. Therefore it is within the range of probability that Curve 8 should be regarded as the result of a single inoculation; that is, 2 c.c. containing 2,000 million *T* and 1,000 million *A* and 1,000 million *B*.

The typhoid agglutinins are unaffected by the first inoculation (inoculating needle probably punctured the bowel and the vaccine was voided) but commence their rise on the third day after the second inoculation and reach the maximum on the eighteenth day after this inoculation. At this point the titer shows no change for the next two days and then falls rapidly (65 per cent.) until the thirty-sixth day when it appears to have reached its point of equilibrium for the subsequent fall is but gradual.



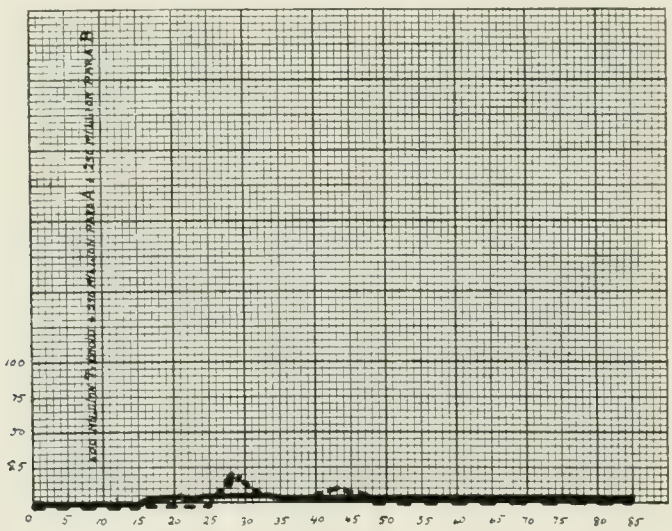
Curve 9

The paratyphoid A agglutinins are not affected by the first inoculation (which was probably voided unabsorbed), but commence their rise on the third day after the second inoculation. The maximum is reached on the tenth day after the second inoculation. The titer then falls rapidly (17 per cent.) until the twelfth day. At this point the titer shows no change until the sixteenth day. From this point until the twenty-fourth day a further rise in titer is noted

(270 per cent.). This latter rise is anomalous and somewhat difficult of explanation. From this point until the thirty-sixth day a fall (69 per cent.) occurs. At this point the curve appears to have reached equilibrium, for the subsequent fall is but gradual.

The paratyphoid B. agglutinins are unaffected by the first inoculation (which was probably voided unabsorbed) but commence their rise on the third day after the second inoculation. The maximum of this rise is reached on the tenth day. From this point the curve falls and then shows no change until the eighteenth day when a fall (50 per cent.) occurs. From this point the curve appears to be in equilibrium, for with the exception of a few small fluctuations the subsequent fall is but gradual.

RABBIT 9.—(Group 5, Curve 9.) *The typhoid agglutinins* showed a slight rise on the fourth day after this inoculation which reached its maximum on the tenth day. The curve shows no further change for the next two days. It then falls, reaching its point of equilibrium on the twenty-eighth day, for from this point until the seventy-seventh day the fall was but gradual.



Curve 10

The paratyphoid A agglutinins show a slight rise on the second day after this inoculation. The titer shows no change for the next three days and then falls, reaching the base line of normal agglutination by the seventh day.

The paratyphoid B agglutinins show no rise above the base line of normal agglutination.

RABBIT 10.—(Group 5, Curve 10.) *The typhoid agglutinins* did not show a rise until the seventh day after the inoculation. From this point they rose to a maximum on the twelfth day. The titer fell on the next two days and then regained its former height and showed no further change until the twenty-fourth day. From the twenty-fourth to thirty-fourth day the titer fell 58 per cent. This was the point of equilibrium for from this point to the seventy-seventh day the fall was but gradual.

The paratyphoid A agglutinins did not rise above the base line of normal agglutination.

TABLE 12.—Data from which Curve 9 Was Plotted

Day of Experiment	Standard Agglutinin Units		
	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B
1	0	0	0
2	0	0	0
3	0	0	0
5	0	0	0
9	Inoculated 0.5 c.c. T A B = 500 million T + 250 million A + 250 million B		
10	0	0	0
11	0	1.38	0
12	0	1.38	0
13	2.5	1.38	0
14	3.5	0.69	0
15	5.0	0.69	0
16	8.41	0.69	0
17	25.0	0.69	0
18	39.4	0	0
19	41.6	0	0
20	41.6	0	0
21	31.2	0	0
22	21.8	0	0
23	21.8	0	0
24	18.7	0	0
25	12.5	0	0
26	12.5	0	0
29	17.7	0	0
32	31.2	0	0
33	25.0	0	0
35	31.25	0	0
37	25.0	0	0
39	25.0	0	0
41	25.0	0	0
43	25.0	0	0
46	21.8	0	0
48	21.8	0	0
50	21.8	0	0
52	21.8	0	0
56	13.8	0	0

TABLE 13.—Data from which Curve 10 Was Plotted

Day of Experiment	Standard Agglutinin Units		
	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B
1	0	0	0
2	0	0	0
3	0	0	0
5	0	0	0
9	0	0	0
9	Inoculated 0.5 c.c. T A B = 500 million T + 250 million A + 250 million B		
10	0	0	0
11	0	0	0
12	0	0	0
13	0	0	0
14	0	0	0
15	0	0	0
16	0.62	0	0
17	1.8	0	0
18	1.8	0	0
19	0.62	0	0
20	1.2	0	0
21	4.38	0	0
22	2.5	0	0
23	2.5	0	0
24	4.38	0	0
25	4.38	0	0
26	4.38	0	3.7
29	4.38	0	18.5
32	4.38	0	2.78
33	4.33	0	1.85
35	3.7	0	0.0
37	0.0	0	0.0
39	2.07	0	3.7
41	0.0	0	0.0
43	1.8	0	9.25
46	1.8	3.2	7.4
48	0.0	0	3.7
50	1.8	0	3.7
52	1.66	0	1.85
86	0.79	0	0.0

The paratyphoid B agglutinins did not show a rise until the seventeenth day after the inoculation. A maximum was reached the next day. A fall then occurred until the twenty-eighth day. On the thirtieth day to thirty-fourth day an increase in paratyphoid *B* titer is noticed. From this point to the forty-third day a fall (80 per cent.) takes place. When examined on the seventy-seventh day there were no paratyphoid *B* agglutinins above the base line of normal agglutination.

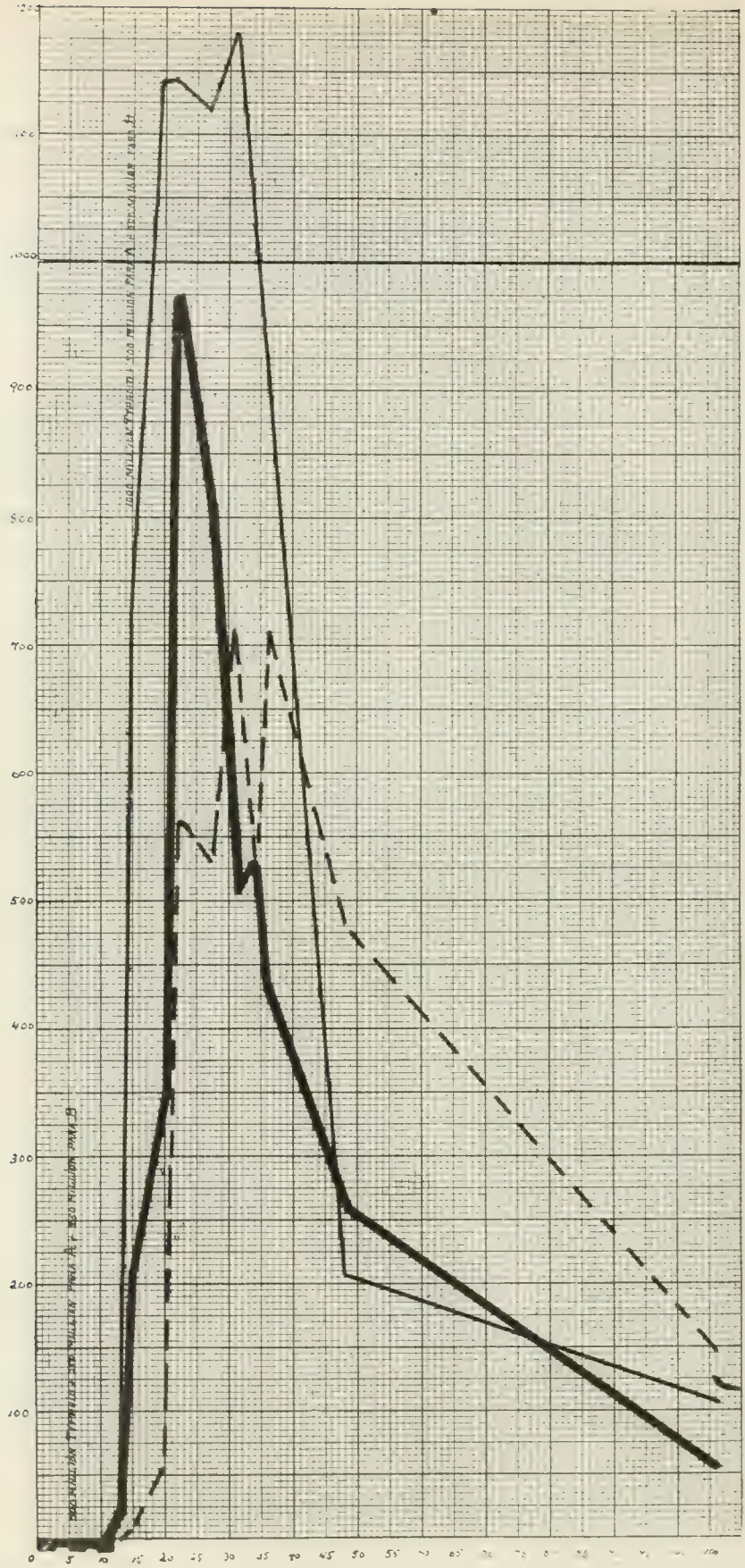
CURVES FROM MEN

None of the men in the following experiments presented any history of a previous infection with *B. typhosus, B. paratyphosus A* or *B. paratyphosus B.* The men of Groups VI to IX, inclusive, presented no history of a previous inoculation with any of these organisms. The blood was always examined once before inoculation to determine the base line of normal agglutination. The local and general reactions to each inoculation, even to the increased dosage in Curves 22 and 23, were in no way severe. The individual on the day following each of the first and second inoculations usually developed a very mild headache, a feeling of "sleepiness" and a slight soreness at the point of inoculation, but this passed away the next day. He was not prevented from going about his usual occupation. In the case of the third and fourth inoculation, the local and general reactions were negligible.

W. G.—(Group 6, Curve 11.) *The typhoid agglutinins* had not commenced to rise on the fourth day but showed a rise on the seventh day following the first triple inoculation. By the ninth day the titer had risen (85 per cent.). At this point the second triple inoculation was given. The curve had continued to rise when examined on the fifth day after this inoculation. The *T* titer reaches its maximum on the seventh day after the second triple inoculation. From this point to the thirty-fourth day the titer falls (74 per cent.).

The paratyphoid A agglutinins had not commenced to rise on the fourth day but showed a rise on the seventh day after the first triple inoculation, which was increased by 2,400 per cent. by the ninth day. At this point the second triple inoculation was given. The *A* titer continued to rise (70 per cent.) by the fifth day. The curve shows no change on the seventh day. A slight fall is noted on the twelfth day. On the sixteenth day a further rise is noted which may be taken as the maximum of the curve. From this point to the thirty-fourth day the titer falls (81 per cent.).

The paratyphoid B agglutinins had not commenced to rise on the fourth and seventh day but showed a rise on the ninth day after the first triple inoculation. At this point the second triple inoculation is given. The curve continued to rise when examined on the fifth and seventh day after the second triple inoculation. On the twelfth day a slight fall in titer is noted, which, as it corresponds with the drop previously described on the same day in the *A* curve, may be of some significance. By the sixteenth day the curve has risen again to a point which may be taken as its maximum. On the nineteenth day a fall to a point equal to that of the twelfth day is noticed, to be followed on the twenty-first day by a rise equal in amount. From this point to the thirty-fourth day the titer falls (25 per cent.). The apparent irregularities in the maximum of this curve may be explained by saying that inasmuch as the irregularities of the paratyphoid curves correspond quite closely, they are due to an actual change in state of the individual. It is also possible that the apex of the *A* titer on the fifth day (after the second inoculation) and the apex of the *B* titer on the seventh day, represent the maximum of



Curve 11

TABLE 14.—Data from which Curve 11 Was Plotted

Day of Experiment	Standard Agglutinin Units		
	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B
1	0	0	0
6	Inoculation, 0.5 c.c. T A B = 500 million T + 250 million A + 250 million B		
10	0	0	0
13	24.1	29.0	0
15	Inoculation, 1.0 c.c. T A B = 1,000 million T + 500 million A + 500 million B		
15	210.0	710.0	5.06
20	344.0	1,142.0	56.0
22	970.0	1,142.0	561.0
27	805.0	1,122.0	532.0
31	510.0	1,180.0	712.0
34	530.0	1,030.0	532.0
36	432.0	927.0	712.0
48	263.0	206.0	476.0
106	56.5	106.0	146.0

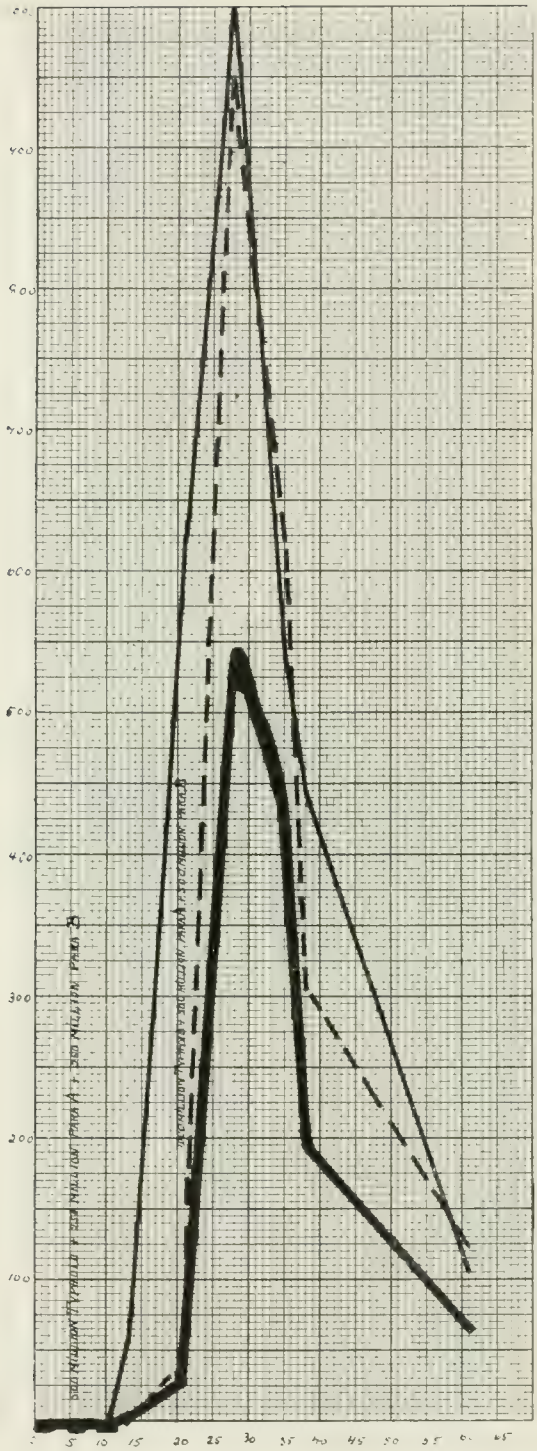
the rises due to the first inoculation. In that case the drop noted on the twelfth day may either be the normal fall in titer following a maximum, or a negative phase. The maximum noted on the sixteenth day would represent the maximum of the rise due to the second inoculation.[30]

J. G. J.—(Group 6, Curve 12.) *The typhoid agglutinins* had not commenced to rise on the fifth day after the first triple inoculation, but showed a slight rise on the seventh day which had greatly increased by the fifteenth day. At this point the second triple inoculation was given. The titer continued rising, reaching a maximum on the seventh day after the last inoculation. From the seventh to fortieth day (after the second triple inoculation) the *T* titer fell (88 per cent.).

The paratyphoid A agglutinins had not commenced to rise on the fourth day after the first triple inoculation, but showed a rise on the seventh day which was greatly increased by the fifteenth day. At this point the second triple inoculation was given. The A titer had reached a maximum when next examined o nthe seventh day after the second triple inoculation. From the seventh to fortieth day the *A* titer fell (89 per cent.).

The paratyphoid B agglutinins had not commenced to rise on the fourth and seventh days, but showed a rise on the fifteenth day. At this point the second triple inoculation was given. The *B* titer had risen to a maximum when next examined on the seventh day. From the seventh to fortieth day the titer fell (87 per cent.).

30. That the maximum of the curve occurs on any given day, or that a negative phase is present or absent, can only be decisively stated when daily examinations of the blood are made, as in the case of the rabbit. In the case of the human subjects, conditions existed which rendered it impossible to take daily samples of blood. Accordingly, it is not possible in their case to determine with certainty the presence or absence of a negative phase on any particular day, or the exact position of the true maxima of their curves.



Curve 12

TABLE 15.—Data from which Curve 12 Was Plotted

Day of Experiment	Standard Agglutinin Units		
	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B
1	0	0	0
6	Inoculation, 0.5 c.c. T A B = 500 million T + 250 million A + 250 million B		
10	0	0	0
13	3.22	57.0	6
21	32.25	622.0	53.3
21	Inoculation, 1.0 c.c. T A B = 1,000 million T + 500 million A + 500 million B		
28	541.0	1,010.0	950.0
35	432.0	539.0	622.0
38	192.0	442.0	304.0
61	64.8	103.0	120.0

The maxima of the *T*, *A*, and *B* curves appear to fall on the same day, instead of the more usual condition as seen in the other curves, namely, that the *B* curve commences its rise and attains its maximum later than the *T* and *A* curves. This is perhaps apparent rather than real and may be due to the long intervals between examinations.

R. F. D. R.—(Group 7, Curve 13.) *The typhoid agglutinins* were not visibly affected by the *A B* inoculations. On the second and fifth days after the first *T* inoculation there was still no rise of *T* agglutinins. This is interesting in that both the *A* and *B* agglutinins showed rises of 68 and 65 per cent., respectively, on the second day after the first *T* inoculation. On the tenth day the second *T* inoculation was given. On the third day after this last *T* inoculation the *T* agglutinins showed a rise which reached its maximum on the twelfth day (after this last *T* inoculation). The *A* and *B* agglutinins also show rises of 2 and 75 per cent., respectively, on the twelfth day. Whether the *A* and *B* curves would have shown a rise to a maximum before the *T* curves, if examinations had been made at shorter intervals, cannot be said with certainty, but judging from the other curves, it may be supposed that they would. From the twelfth to the sixty-first day the *T* titer fell 94 per cent.

The paratyphoid A agglutinins had not commenced to rise on the fifth day after the first *A B* inoculation but showed a marked rise on the seventh day, which was increased by the ninth day. At this point the second *A B* inoculation was given. The *A* titer continued to rise to a maximum four days later, that is, fourteenth day after the first inoculation. A fall (7 per cent.) occurs on the seventeenth day. It may be assumed that the maximum of the *A* curves on the fourteenth day is that of the rise due to the first inoculation, even though it occurs four days after the second inoculation. Whether the fall that is noted on the seventeenth day is the fall usually seen after the maximum of a single inoculation curve is attained, or whether it is the negative phase following the second inoculation, or whether again it is a combination of the two, cannot be decisively determined in this particular instance.

The *A* titer has commenced its new rise due to the second inoculation and attained its maximum on the ninth day after the second inoculation (nineteenth day after the first inoculation). From this point until the twenty-first day the *A* titer falls 82 per cent. where it is in equilibrium, for the titer shows no change on the twenty-third day. At this point the first *T* inoculation is given. This evidently stimulates the production of the *A* agglutinins for the

titer has risen (68 per cent.) by the second day after this last inoculation. A fall that is slightly greater than this rise is noted on the fifth day. The second *T* inoculation is given on the ninth day. Three days later no rise in *A* agglutinins is noted; in fact, they have decreased slightly since the last inoculation. Whether this fall is a negative phase following the last *T* inoculation or whether it is the natural, gradual fall cannot be decisively stated. Twelve days after this last *T* inoculation the titer has increased (2 per cent.). From this point until the sixty-first day the *A* titer falls 60 per cent.

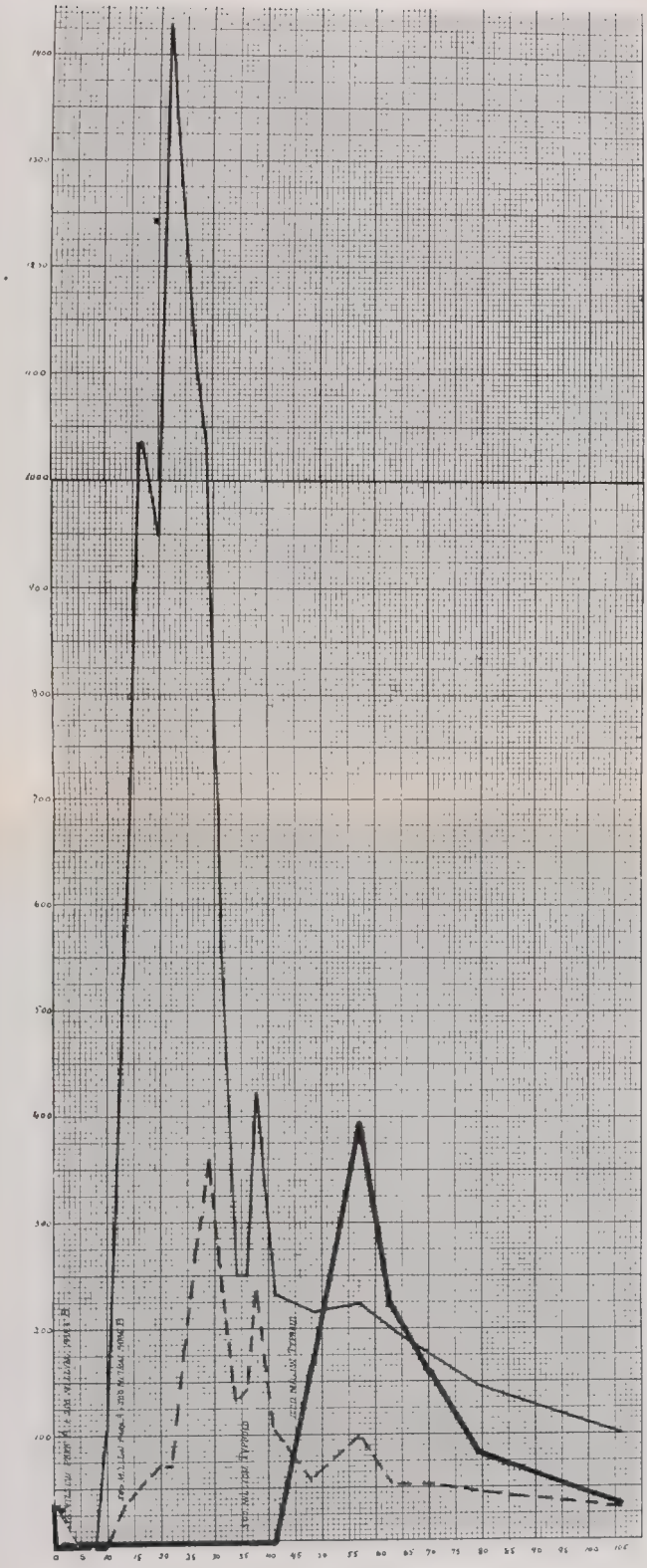
TABLE 16.—DATA FROM WHICH CURVE 13 WAS PLOTTED

Day of Experiment	Standard Agglutinin Units		
	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B
1	0	0	0
3	Inoculated, 0.5 c.c. A B = 250 million A + 250 million B		
8	0	0	0
10	0	103.5	0
18	0	531.0 - 250.0	34.2
13	Inoculated, 1.0 c.c. A B = 500 million A + 500 million B		
17	0	1,035.0	56.0
20	0	950.0	71.5
22	0	1,428.0	71.5
27	0	1,100.0	285.0
29	0	1,032.0	357.0
31	0	590.0	264.0
34	0	250.0	132.2
36	0	250.0	142.3
36	Inoculated, 0.5 c.c. T = 500 million T		
38	0	421.0	235.0
41	0	235.0	107.2
45	Inoculated, 1.0 c.c. T = 1,000 million T		
48	162.0	218.0	56.0
57	390.0	224.0	95.0
63	223.0	200.0	51.0
70	162.0	179.0	53.0
79	84.0	148.5	47.8
106	32.5	100.0	27.0

The paratyphoid B agglutinins had not commenced to rise on the fifth day after the first *A B* inoculation, but showed a very slight rise on the seventh day. This was increased by the tenth day. At this point the second *A B* inoculation was given. The *B* titer continued to rise. The plateau seen on the seventh to ninth day after the second inoculation may represent the maximum of the rise due to the first inoculation and the subsequent negative phase following the second inoculation. The maximum of the rise due to the second inoculation was reached on the sixteenth day (after the second inoculation; the twenty-sixth day after the first inoculation). From this point

until the twenty-third day (after the second inoculation) the titer fell (45 per cent.). On the twenty-third day the titer had risen slightly. At this point the first *T* inoculation was given. This evidently stimulated the *B* agglutinins, for by the second day after this inoculation the *B* titer had risen 55 per cent. From this point until the fifth day after this last inoculation the *B* titer fell 64 per cent. The second *T* inoculation was given on the tenth

as that of the rise due to the second inoculation was attained on the sixteenth day. By the twenty-fifth day after this last inoculation the *B* titer fell 53 per cent. At this point the first *T* inoculation was given. The *B* titer showed a slight fall by the third day after this first *T* inoculation, and a still greater drop by the fifth day. On the tenth day the *B* titer showed a rise (150 per



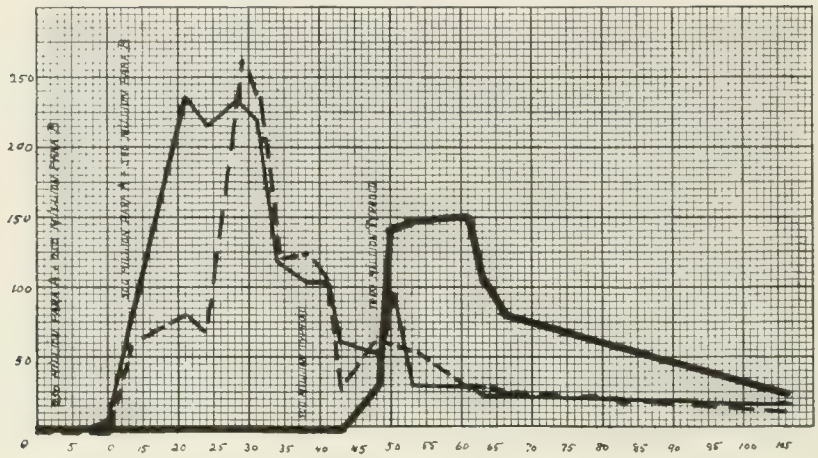
Curve 13

until the twenty-third day (after the second inoculation) the titer fell (45 per cent.). On the twenty-third day the titer had risen slightly. At this point the first *T* inoculation was given. This evidently stimulated the *B* agglutinins, for by the second day after this inoculation the *B* titer had risen 55 per cent. From this point until the fifth day after this last inoculation the *B* titer fell 64 per cent. The second *T* inoculation was given on the tenth day. On the third day after this second inoculation the *B* titer showed a distinct drop (20 per cent.), but no examination was possible on the tenth when the second *T* inoculation was given, owing to the loss of the blood specimen by the breaking of a faulty centrifuge tube. It is therefore impossible to decide in this instance whether this further fall in titer just mentioned was a true negative phase or whether it represented the normal fall in titer. On the twelfth day after this second *T* inoculation, the *B* titer showed a rise of 75 per cent., evidently in response to the stimulation of the last *T* inoculation. By the eighteenth day after this second *T* inoculation the *B* titer fell 46 per cent. As the subsequent fall in titer was but gradual from this point until the sixty-first day (after the second *T* inoculation) it may be assumed that the curve had reached its point of equilibrium.

H. W. T.—(Group 7, Curve 14.) *The typhoid agglutinins* were not apparently affected by either of the *A B* inoculations and did not show a rise until the tenth day after the first *T* inoculation. At this point the second *T* inoculation was given. The *T* titer shows a marked rise on the second day after this last inoculation, reaching a maximum on the thirteenth day. From this point until the eighteenth day the curve shows a fall of 43 per cent. When next examined on the fifty-eighth day the *T* titer had fallen an additional 40 per cent.

The paratyphoid A agglutinins had not commenced to rise on the fifth day after the first *A B* inoculation but showed a rise on the seventh day which had greatly increased by the tenth day. At this point the second *A B* inoculation was given. When next examined on the eighth day after this last inoculation the *A* titer had risen 300 per cent., which may possibly be the maximum of the rise due to the first inoculation. On the eleventh day the *A* titer had fallen slightly (possibly a negative phase following the second inoculation) but regained its former height on the sixteenth day (possibly the maximum of the rise due to the second *A B* inoculation). From this point until the twenty-fifth day the *A* titer fell 57 per cent. At this point the first *T* inoculation was given. By the third day the *A* titer had risen slightly, evidently stimulated by the *T* inoculation. From this point until the tenth day the *A* titer fell 48 per cent. At this point the second *T* inoculation was given. The *A* titer showed a rise of 75 per cent. on the second day after this inoculation. From this point until the fifth day the *A* titer fell 85 per cent. The curve then shows but a small decrease until the eighteenth day, indicating that the titer had reached its point of equilibrium. When next examined on the fifty-eighth day the *A* titer showed an additional fall of 11 per cent.

The paratyphoid B agglutinins had not commenced to rise on the fifth and seventh days after the first *A B* inoculations, but showed a rise on the tenth day. At this point the second *A B* inoculation was given. By the eighth day after this last inoculation, that is, the eighteenth day after the first inoculation, the *B* titer had risen 117 per cent., which may be considered as the maximum of the rise due to the first inoculation. On the eleventh day after the second inoculation a fall was noted which may represent the negative phase following the second inoculation. A rise to a maximum which may be considered as that of the rise due to the second inoculation was attained on the sixteenth day. By the twenty-fifth day after this last inoculation the *B* titer fell 53 per cent. At this point the first *T* inoculation was given. The *B* titer showed a slight fall by the third day after this first *T* inoculation, and a still greater drop by the fifth day. On the tenth day the *B* titer showed a rise (150 per



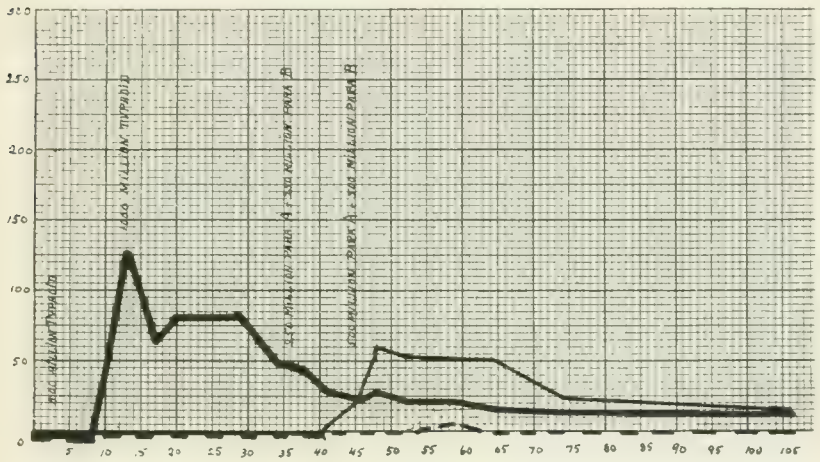
Curve 14

TABLE 17.—Data from which Curve 14 Was Plotted

Day of Experiment	Standard Agglutinin Units		
	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B
1	0	0	0
3	Inoculated, 0.5 c.c.	A B = 250 million A + 250	million B
8	0	0	0
10	0	2.85	0
13	Inoculated, 1.0 c.c.	A B = 500 million A + 500	million B
21	0	235.0	128.0
24	0	215.0	118.7
29	0	235.0	265.0
31	0	218.0	237.0
34	0	118.0	122.0
38	0	102.7	125.0
38	Inoculated, 0.5 c.c. T = 500 million T		
41	0	103.0	107.0
43	0	59.0	25.0
48	27 7	53.0	64.0
48	Inoculated, 1.0 c.c. T = 1,000 million T		
50	139.0	98.5	59.0
53	144.0	29.5	53.2
61	149.0	28.5	25.5
63	104.0	24.2	27.0
66	84.0	24.2	25.0
106	24.2	18.3	10.85

cent.). Whether or not this rise would have been found to occur earlier if the intervals between examinations had been shorter cannot be decisively stated. At this point the second *T* inoculation was given. The *B* titer shows no further rise. Whether or not a rise may have occurred during one of the intervals when the blood was not examined, cannot be decisively stated. By the thirteenth day after this last *T* inoculation the *B* titer had fallen 66 per cent. and as it showed no change from this point until the eighteenth day it may be assumed that this curve had reached its point of equilibrium. When next examined on the fifty-eighth day the *B* titer had fallen an additional 14 per cent.

T. P.—(Group 8, Curve 15.) *The typhoid agglutinins* had not commenced to rise on the fifth day after the first *T* inoculation, but showed a rise on the seventh day which was greatly increased by the tenth day, which appears to have been the maximum. At this point the second *T* inoculation was given. On the fourth day after this last inoculation the *T* titer fell (50 per cent.; that is, a negative phase). On the seventh day the titer showed a rise of 27 per cent. The curve shows no change when examined on the eleventh and sixteenth days. From the sixteenth to twenty-third day the *T* titer fell 41



Curve 15

per cent. At this point the first *A B* inoculation was given. The *T* titer showed only a small drop (6 per cent.). By the fifth day a further drop of 36 per cent. had occurred. By the tenth day the titer had fallen still farther. At this point the second inoculation is given. On the third day after this last inoculation the *T* titer evidently stimulated by the *A B* inoculation shows a rise of 19 per cent. From this point until the nineteenth day the *T* titer fell 37 per cent. As the titer showed but a very gradual fall from this point until the sixty-first day after the last inoculation, it may be assumed that it had reached its point of equilibrium.

The paratyphoid A agglutinins did not show a rise until the fifth day after the first *A B* inoculation, which was greatly increased by the tenth day. At this point the second *A B* inoculation was given. The titer showed a rise of 150 per cent. by the third day after this last inoculation, which appears to be the maximum. By the seventh day a fall of 14 per cent. had occurred. From this point until the nineteenth day the curve showed little change. From the nineteenth to twenty-ninth day a fall of 52 per cent. had occurred. When next examined on the sixty-first day after the last inoculation an additional fall of 28 per cent. had occurred.

TABLE 18.—Data from which Curve 15 Was Plotted

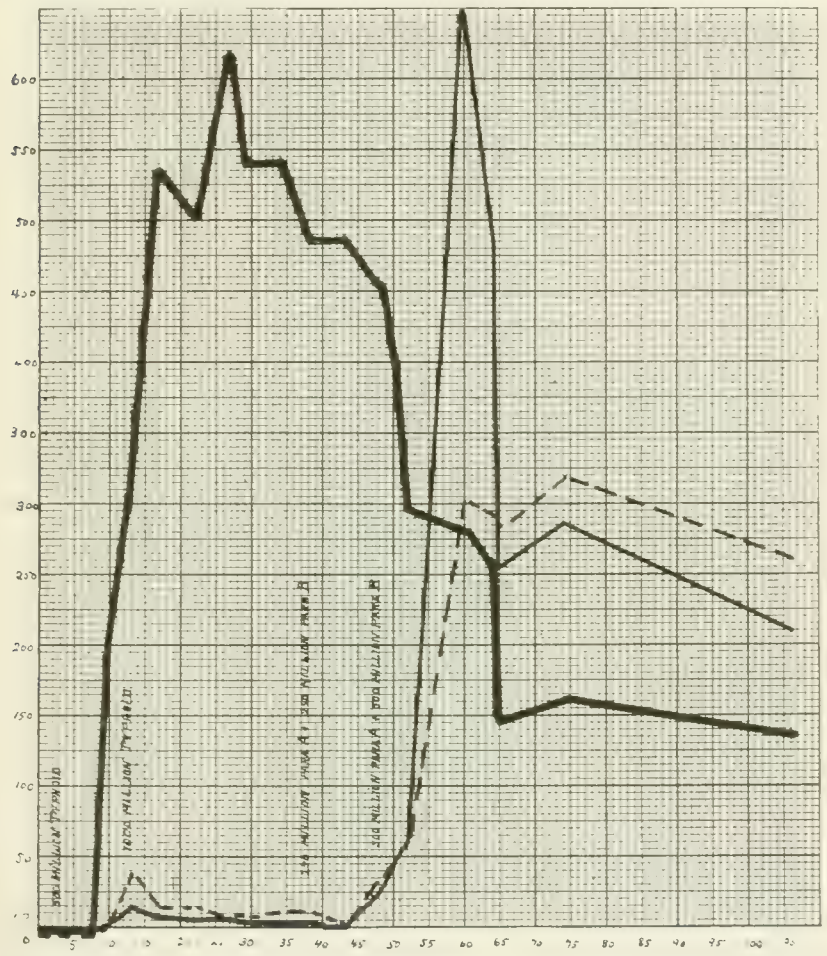
Day of Experiment	Standard Agglutinin Units		
	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B
1	0	0	0
3	Inoculated, 0.5 c.c. T = 500 million T		
8	0	0	0
10	40.3	0	0
13	126.0	0	0
13	Inoculated, 1,000 million T		
17	63.0	0	0
20	80.1	0	0
24	80.1	0	0
29	32.5 - 80.1	0	0
31	64.9	0	0
34	48.6	0	0
36	46.5	0	0
36	Inoculated, 0.5 c.c. A B = 250 million A + 250 million B		
38	43.0	0	0
41	29.1	2.06	0
45	22.6	23.6	0
45	Inoculated, 1.0 c.c. A B = 500 million para A + 500 million para B		
52	27.0	59.0	0
52	22.0 128.0	51.5	0
59	23.7 20.2	51.5	5.31
64	14.15	50.0	0
74	13.8	24.0	0
106	11.9	24.0	0

The paratyphoid B agglutinins did not show a rise until the fourteenth day after the second *A B* inoculation, which appears to be the maximum. By the nineteenth day the *B* titer had fallen to the base line of normal agglutination where it remained for all subsequent examinations. The only rise of the agglutinins of the first organism (that is, *T*) which can be attributed to the *A B* inoculations was one that occurred on the same day as the maximum of the *A* curve (one of the organisms inoculated later). The very late and slight rise of the *B* curve is anomalous and is somewhat difficult of explanation.

E. A. W.—(Group 8, Curve 16.) In Curve 16, E. A. W. gave no history of a previous infection or inoculation with *B. typhosus, B. paratyphosus A* or *B. paratyphosus B,* although from the readiness with which the *A* and *B* agglutinins respond to the *T* inoculation, it might appear there had been some previous undiagnosed infection by these two organisms, unless we have here an instance of abnormal sensitiveness of the mechanism for the formation of antibodies.

The typhoid agglutinins had not commenced to rise on the fifth day after the first *T* inoculation, but showed a marked rise by the seventh day. This

was further increased by the tenth day. At this point the second *T* inoculation was given. By the fourth day after this last *T* inoculation the *T* titer had risen 77 per cent. By the ninth day the *T* titer showed a fall of 6 per cent. The curve up to this point may be interpreted variously. As has been noted above, the maximum of the rise due to the first inoculation may occur in one of three places: (1) before the second inoculation, (2) after the second



Curve 10

inoculation, or (3) may be fused, as it were, with the rise due of the second inoculation, depending on the length of the interval between the two inoculations. In this case, it appears that the second of these possibilities has occurred and that the *T* apex on the fourth day after the second *T* inoculation is the maximum of the rise due to the first inoculation and that the fall noted on the ninth day after the second inoculation is the negative phase following the second inoculation. By the fourteenth day after the second inoculation the new rise had commenced and had attained its maximum. By the sixteenth day the *T* titer had fallen 12 per cent. The curve shows no

TABLE 19.—Data from which Curve 16 Was Plotted

Day of Experiment	Standard Agglutinin Units		
	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B
1	0	0	0
3	Inoculation, 0.5 c.c. T = 500 million B. typhosus		
8	0	0	0
10	200	2.85	1.43
13	298	15.0	37.5
13	Inoculation, 0.5 c.c. T = 1,000 million B. typhosus		
17	535	7.15	12.8
22	500	5.7	14.15
27	620	5.0	5.7
29	540	3.78	5.7
31	540	3.78	6.4
34	540	3.55	9.5
38	486	3.55	11.9
38	Inoculation, 0.5 c.c. A B = 250 million para A + 250 million para B		
41	486	2.29	5.7
43	486	1.19	2.86
48	454	0.25	27.4
48	Inoculation, 1.0 c.c. A B = 500 million para A + 500 million para B		
50	405	44.1	43.0
52	296	59.0	62.1
60	278	648.0 - 768.0	302.0
64	255	476.0	292.0
65	148	252.0	284.0
74	162	286.0	319.0
106	138	210.0	263.0

change on the eighteenth and twenty-first days. By the twenty-fifth day the *T* titer had fallen another 8 per cent. At this point the first *A B* inoculation was given.

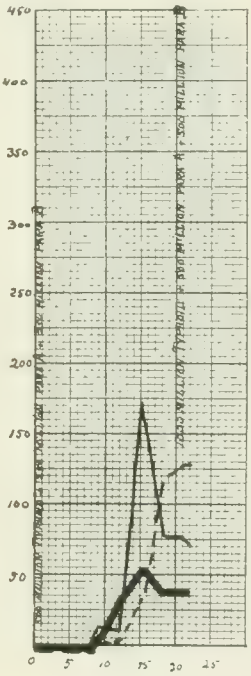
The *T* agglutinins were possibly affected by this first *A B* inoculation for they showed no change (that is, did not continue their natural fall) when examined on the third and fifth days (after this first *A B* inoculation). On the tenth day the *T* titer had fallen 6 per cent. At this point the second *A B* inoculation was given but no effect was seen in the *T* titer. From this point until the seventeenth day (after this last inoculation) the *T* titer fell (65 per cent.). The fall in titer from the seventeenth to fifty-eighth day was very gradual, indicating that it had reached its point of equilibrium.

The paratyphoid A agglutinins did not commence to rise until the seventh day after the first *T* inoculation and reached a maximum on the tenth day. At this point the second *T* inoculation was given. The *A* titer had fallen 50 per cent. by the fourth day after this last inoculation. From this point until the twenty-fifth day after this last *T* inoculation the *A* titer showed little

change. At this point the first *A B* inoculation was given. On the third and fifth days after this a drop was seen (that is, negative phase). On the tenth day a marked rise had occurred. At this point the second *A B* inoculation was given. The curve continued its rise reaching its maximum on the twelfth day. From the twelfth to seventeenth day a rapid fall (65 per cent.) occurred. The fall in titer from the seventeenth to twenty-sixth day was very gradual, indicating that it had reached its point of equilibrium.

The paratyphoid B agglutinins behaved in exactly the same way as the *T* and *A* agglutinins, their maxima and negative phases occurring on the same days.

W. C. C.—(Group 9, Curve 17.) *The typhoid agglutinins* first show a slight rise on the eighth day after the first triple inoculation and reach their maximum on the fourteenth day. On the seventeenth day a fall (25 per cent.) is recorded. On the twentieth day no change in the typhoid titer is noted. The



Curve 17

second inoculation is given at this point. On the following day no change is noted (that is, no negative phase). It was impossible to examine the blood for an interval of thirty-eight days. By this time the *T* titer had fallen and any rise due to the second triple inoculation was missed.

The paratyphoid A agglutinin, like the T agglutinin, show a rise on the eighth day after the first inoculation, which reaches its maximum also on the fourteenth day. By the seventeenth day the titer has fallen (56 per cent.) and shows no change on the twentieth day. At this point the second inoculation is given. On the following day a slight fall in titer (that is, a negative phase) is noted. It was impossible to examine the blood for an interval of thirty-eight days. By this time the *A* titer had fallen and any rise due to the second inoculation was missed.

TABLE 20.—Data from which Curve 17 Was Plotted

Day of Experiment	Standard Agglutinin Units		
	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B
1	0	0	0
1	Inoculated, 0.5 c.c. T A B = 500 million T + 250 million A + 250 million B		
8	0	0	0
9	1.3	11.8	1.43
12	32.4	9.8	2.85
15	53.0	172.0	21.6
18	38.9	76.1	53.0 - 96.0 - 119.0
21	37.1	76.1	127.8
21	Inoculated, 1.0 c.c. T A B = 1,000 million T + 500 million A + 500 million B		
22	37.1	71.5	127.8
60	28.0	57.0	600.0

The paratyphoid B agglutinins showed a very slight rise on the eighth day after the first inoculation, which reached its maximum on the twentieth day; when the second inoculation was given. The titer shows no change the next day. It was impossible to examine the blood for an interval of thirty-eight days. The *B* titer then showed a marked rise. It will be noted that in common with most of the other experiments the *B* curve attained its maximum later than the *T* and *A* curves.

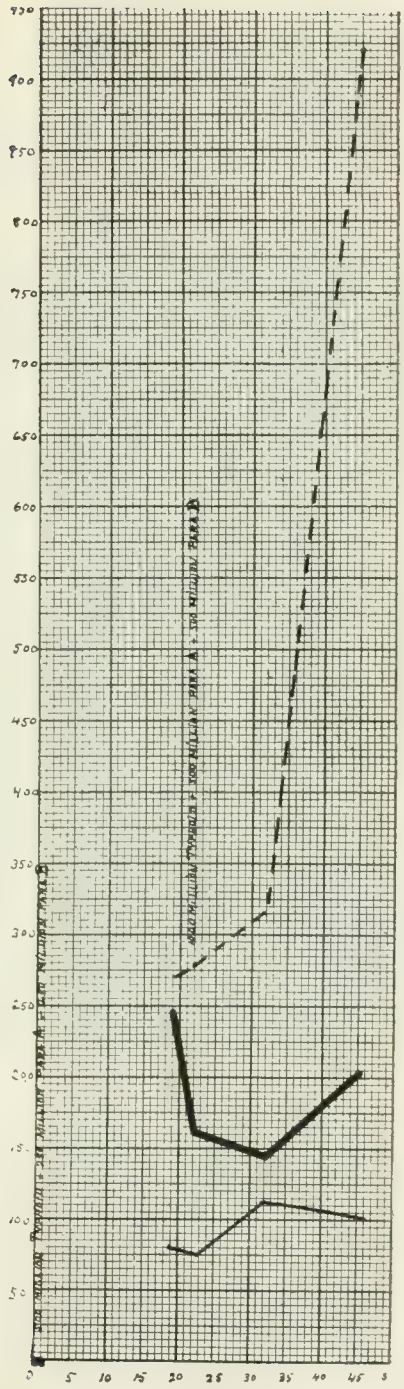
F. H. M.—(Group 9, Curve 18.) When first examined on the nineteenth day after the first triple inoculation the *typhoid agglutinins* had evidently attained their maximum, for on the twenty-first day the titer had fallen (33 per cent.). At this point the second inoculation was given.

The *T* titer showed a fall (8 per cent.; possibly a negative phase) when examined on the tenth day (after the second inoculation). On the twenty-third day a rise in the *T* titer (36 per cent.) was noted.

The paratyphoid A agglutinins, like the *T* agglutinins, have reached their maximum on the nineteenth day and show a fall (5 per cent.) on the twenty-first day. At this point the second inoculation was given. By the tenth

TABLE 21.—Data from which Curve 18 Was Plotted

Day of Experiment	Standard Agglutinin Units		
	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B
1	0	0	0
1	Inoculated, 0.5 c.c. T A B = 500 million T + 250 million A + 250 million B		
19	244.0	80.0	271.5
22	162.1	75.6	281.0
22	Inoculated, 1.0 c.c. T A B = 1,000 million T + 500 million A + 500 million B		
32	148.0	114.0	320.0
45	102.0	100.0	920.0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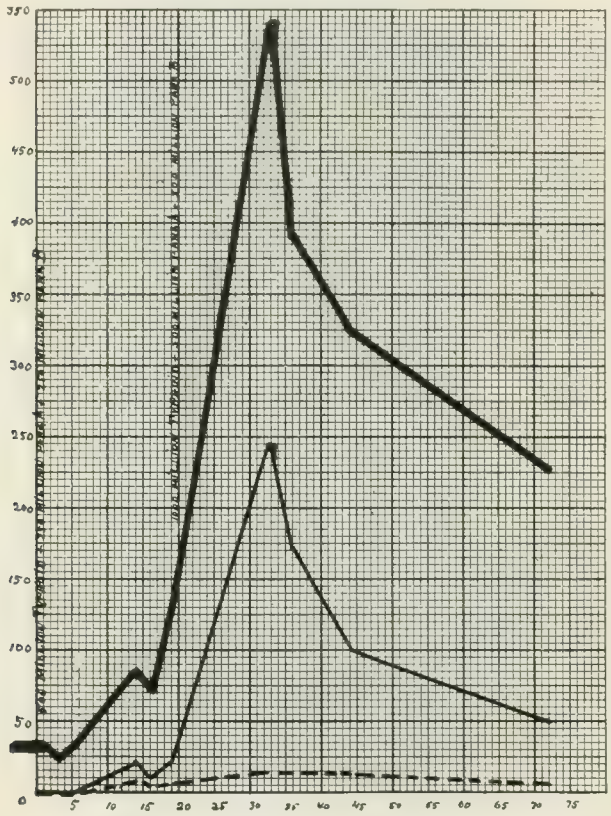
Curve 18

day after the second inoculation the *A* titer had risen (40 per cent.). By the twenty-third day a fall of 10 per cent. had occurred.

The paratyphoid B agglutinins showed a marked rise on the nineteenth day, which is further increased on the twenty-first. The *B* titer showed a marked rise on the tenth day after the second inoculation, which was greatly increased by the twenty-third day. It will also be noted here that the *B* curve attains its maximum last.



Curve 19

J. W.—(Group 10, Curve 19.) *The typhoid agglutinins* when examined four months after the last inoculation had fallen to 39 standard agglutinin units; this was the point of equilibrium, for examinations made one month and six months later showed only a small decrease. After this last examination, that is, ten months after the last inoculation, the first triple inoculation was given. Two days later a negative phase was seen. *On the fifth day* the typhoid titer had commenced to rise, continuing until the fourteenth day. On the sixteenth day a fall is seen similar to that seen in the *A* and *B* curves at this point, but on the nineteenth day the curve continues its rise. At this point the second triple inoculation was given. The typhoid titer had reached its maximum by the fourteenth day after this last inoculation. From the fourteenth to fifty-first day the titer fell (60 per cent.); the fall at first being rapid but later becoming more gradual.

The paratyphoid A agglutinins did not show a rise until the fourteenth day after the first triple inoculation. After a fall on the sixteenth day similar to that seen in the *T* and *B* curves at this point, the titer showed a further rise on the nineteenth day. At this point the second triple inoculation was given. The titer had reached its maximum by the fourteenth day after this last inoculation. From the fourteenth to fifty-first day there is a fall of 80 per cent.

The paratyphoid B agglutinins do not show a rise until the fourteenth day after the first triple inoculation. On the sixteenth day a fall is seen similar to that seen in the *T* and *A* curves at this point. On the nineteenth day the curve has recommenced its rise. At this point the second triple inoculation

TABLE 22.—DATA FROM WHICH CURVE 19 WAS PLOTTED

Day of Experiment	Standard Agglutinin Units		
	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B
1	30.0*	0	0
1	Inoculation, 0.5 c.c. T A B = 500 million T + 250 million A + 250 million B		
3	24.20	0	0
6	32.4	0	0
15	84.2	20.7	31.25
17	65.0	10.82	21.0
20	130.0	22.6	30.0
20	Inoculation, 1.0 c.c. T A B = 1,000 million T + 500 million A + 500 million B		
24	54.1	244.0	12.78
27	390.0	171.5	9.58 - 12.78
45	325.0	100.0	11.18
71	227.0	50.0	5.58

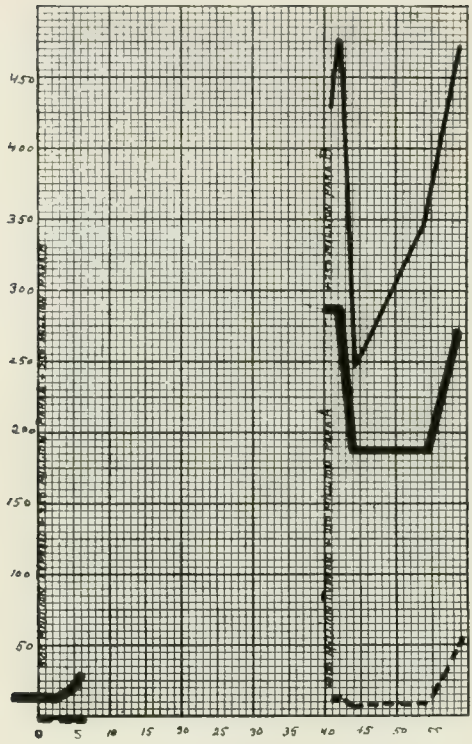
* Immunized with two doses of B. typhosus vaccine (first, 500 million, second, 1,000 million) ten months previous to present experiment.

is given. The titer has reached its maximum by the fourteenth day after this last inoculation. From the fourteenth to twenty-fifth day there is little change showing that the curve has reached its point of equilibrium. From the twenty-fifth to fifty-first day the *B* titer shows a fall of 45 per cent.

This curve is of interest for it plainly shows a negative phase in the persistent typhoid agglutinins resulting from the first triple inoculation. It cannot be contended here, as might be done in the case of falling curves, that this fall was the normal fall in titer, for the typhoid titer had been practically stationary for over six months; three examinations at intervals of two months having shown only a very slight gradual fall.

E. H. N.—(Group 10, Curve 20.) Thirty-two months after the last *T* inoculation, the *typhoid agglutinins* had fallen to 13.8 standard agglutinin units. At this point the first triple inoculation was given. The typhoid titer had risen 17 per cent. the third day (no negative being seen), and by the fifth day the typhoid agglutinins were double the amount recorded at the time of the first triple inoculation. I shall discuss later the significance of this quick response to reinoculation by the typhoid agglutinins in previously inoculated men.

The next examination made on the fortieth day showed that the typhoid titer had risen 960 per cent. At this point the second triple inoculation was



Curve 20

TABLE 23.—Data from which Curve 20 Was Plotted

Day of Experiment	Standard Agglutinin Units		
	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B
1	13.8*	0	0
1	Inoculated, 0.5 c.c. T A B = 500 million T + 250 million A + 250 million B		
4	16.25	0	0
6	27.0	0	0
41	260.0	427.0	10.2
41	Inoculated, 1.0 c.c. T A B = 1,000 million T + 500 million A + 500 million B		
42	260.0	475.0	12.8
44	162.1	244.0	5.1
54	162.1	344.0	6.4
59	242.0	475.0	55.5

* Immunized with three doses of B. typhosus vaccine (first, 500 million; second, 1,000 million; third, 1,000 million) at weekly intervals, thirty-two months previous to present experiment.

given. The next day revealed no change in typhoid titer, but on the third day after the last inoculation the typhoid titer had fallen (62 per cent.; that is, a negative phase). On the thirteenth day the titer showed no change, but on the eighteenth day it had risen 30 per cent.

The paratyphoid A agglutinins showed no rise for the first five days, but when examined on the fortieth day a large rise was noted. At this point the second triple inoculation was given. The titer showed a slight rise on the following day. A fall of 48 per cent. was noted on the second day (negative phase). On the thirteenth day the *A* titer showed a rise of 26 per cent., which was increased to 47 per cent. by the eighteenth day.

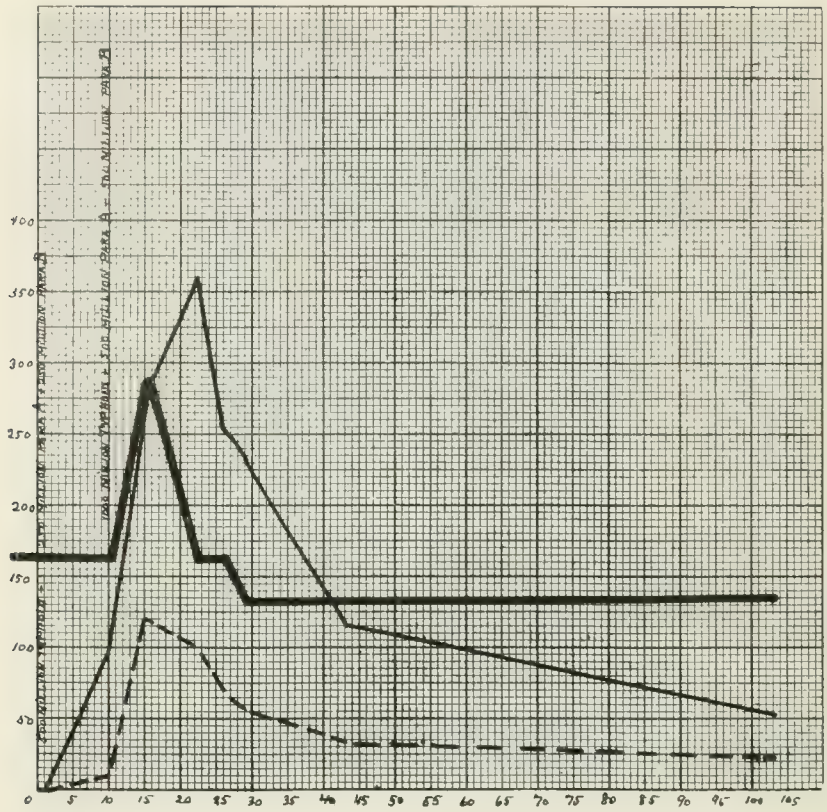
The paratyphoid B agglutinins like the *A* agglutinins had not commenced to rise during the first five days. When examined on the fortieth day the titer showed a marked rise. The second triple inoculation was given at this point. No change in titer was noted on the next day. On the second day a fall of 52 per cent. is shown (negative phase). On the thirteenth day the *B* titer shows a rise which is much increased by the eighteenth day.

E. F. H.—(Group 10, Curve 21.) When examined twenty-two months after the last *T* inoculation the *T* agglutinin titer had fallen to 161 standard agglutinin units. The first triple inoculation was then given. The blood was next examined after an interval of nine days and no change in titer was found. Whether or not the curve had remained stationary during this interval or whether a negative phase had occurred, or whether a quick rise followed by a fall had taken place, cannot be determined from these observations. As it stands this curve would appear to form an exception to the general conclusion arrived at below, that the agglutinins in a previously inoculated individual react more quickly to reinoculation than do the agglutinins of an individual not previously inoculated. Another explanation is, however, more probable as will be seen later. At this point, that is, the ninth day after the first triple inoculation, the second inoculation was given. On the fifth day thereafter, the typhoid titer showed a rise of 82 per cent. A fall of equal amount followed by the twelfth day. Now if the blood had not been examined for an interval of twelve days after the second triple inoculation, the curve would then have appeared to have remained stationary, though, as a matter of fact, it had undergone a marked rise and fall, for the rise would have been missed in the interval. Hence it is possible to suppose that a similar condition following the first triple inoculation was missed in the interval between the examinations, and that instead of a stationary curve as we appear to have, the rise and subsequent fall were completed between the two successive observations. *T* titer then gradually falls until the nineteenth day. From this point the curve appears to be in equilibrium, for little change is noted.

The paratyphoid A agglutinins show a rise on the ninth day (after the first triple inoculation). At this point the second triple inoculation was given. The paratyphoid *A* curve continues to rise unbroken (no negative phase being seen, although an examination was made two days after the second inoculation). The maximum was attained on the twelfth day. The curve is one of the few cases in which it appears that the paratyphoid *A* curve has reached its maximum later than the *T* or *B* curves. This appearance, however, may be artificial and due to the fact that the three actual maxima may all have occurred during the interval from the fifth to fourteenth day from the second triple inoculation, so that all are already falling at the next observation.

In the twelfth to ninety-third day, the *A* titer fell 85 per cent., the fall at first being rapid and later becoming more gradual.

The paratyphoid B agglutinins show a slight rise on the ninth day after the first triple inoculation. At this point the second triple inoculation is given. The *B* titer reaches its maximum on the fifth day after the second triple inoculation. From this point to the ninety-third day the curve falls (75 per cent.), the drop at first being rapid and later being more gradual.



Curve 21

TABLE 24.—Data from which Curve 21 Was Plotted

Day of Experiment	Standard Agglutinin Units		
	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B
1	161.1*	0	0
1	Inoculation, 0.5 c.c. T A B = 500 million T + 250 million A + 250 million B		
10	161.1	94.1	10.7
10	Inoculation, 1.0 c.c. T A B = 1,000 million A + 500 million A + 500 million B		
15	286.0	285.0	119.0
22	161.1	357.5	100.0
26	162.1	251.0	71.5
29	130.0	232.0	57.0
43	130 0	118.0	32.5
103	138.0	50.0	23.6

* Immunized with three doses of B. typhosus vaccine (first, 500 million; second, 1,000 million; third, 1,000 million) twenty-two months previous to present experiment.

The fact that the *B* agglutinins attain their maximum on the same day as the *T* agglutinins is worthy of note, although it must not be forgotten that this as well as the fact that the respective maxima have occurred between the ninth and the fourteenth day (from the second triple inoculation) and so have been missed.

A. D. G.—(Group 11, Curve 22.) *The typhoid agglutinins* eight months after the first inoculation (that is, the *T* inoculation) had fallen to 10 standard agglutinin units. When next examined, six months later, the *T* titer had not appreciably changed. At this point the first triple inoculation was given. Six days after this the *T* titer had risen 2,000 per cent. This quick rise of the *T* agglutinins is of interest, for in men not previously inoculated with *T*, the *T* titer does not begin to rise until the seventh to eighth day, and the maximum is not attained until about the fourteenth to twenty-first day. The significance of this will be discussed later.

TABLE 25.—Data from which Curve 22 Was Plotted

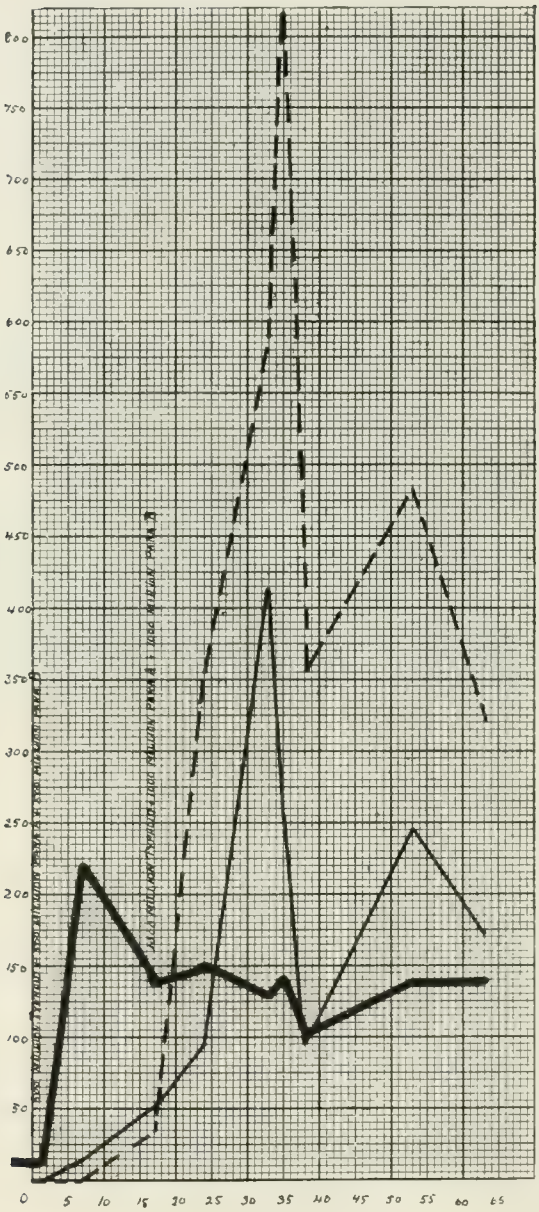
Day of Experiment	Standard Agglutinin Units		
	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B
1	10.22*	0	0
1	Inoculation, 0.5 c.c. T A B = 500 million T + 500 million A + 500 million B		
7	219.0	13.2	0
17	138.0	51.6	35.6
17	Inoculation, 1.0 c.c. T A B = 1,000 million T + 1,000 million A + 1,000 million B		
24	148.0	94.5	356.0
33	130.0	412.0	592.0
35	142.1	252.0	817.0
38	104.0	98.0	356.0
53	138.0	245.0	476.0
63	138.0	172.0	320.0

* Immunized with one dose of B. typhosus vaccine (1,000 million) fourteen months previous to present experiment.

On the sixteenth day (after the first triple inoculation) the *T* titer had fallen (33 per cent.). At this point the second triple inoculation was given. The titer had risen 7 per cent. when examined seven days later. On the sixteenth day after the second triple inoculation the titer had fallen (13 per cent.). On the eighteenth day after the second triple inoculation the titer shows a new rise (9 per cent.). On the twenty-first day the titer has again fallen (26 per cent.). From this point the curve is irregular and difficult of explanation, but judging from the fact that the *A* and *B* curves show the same phenomena, they must be significant. On the eighteenth day (after the second triple inoculation) the *T* curves show a new rise, to be followed on the thirty-sixth day by a decided rise. The titer shows no change on the forty-sixth day. The decided rise from the twenty-first to the thirty-sixth day (after the second triple inoculation) is somewhat difficult to explain, but since the same phenomenon is recorded in both the *A* and *B* curves, it must be significant.

The paratyphoid A agglutinins show a slight rise on the sixth day which reaches its maximum on the sixteenth day.

At this point the second inoculation is given. The titer shows an increase on the seventh day which reaches its maximum on the sixteenth day after the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150
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50
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5
10
15
20
25
30
35
40
45
50
55
60
65

Curve 22

second inoculation. From the sixteenth to eighteenth day (after the second triple inoculation; thirty-second to thirty-fourth day after the last triple inoculation), the *A* titer falls 39 per cent.

A further fall (36 per cent.) recorded during the next three days (thirty-seventh day after the first triple inoculation and twenty-first day after the second triple inoculation). On the thirty-sixth day after the second triple inoculation a rise (140 per cent.) is noted; the same phenomenon as has been recorded in this curve for the *T* agglutinins. On the forty-sixth day from the second triple inoculation the *A* titer has fallen 30 per cent.

A rise in the *paratyphoid B titer* was not recorded until the sixteenth day after the first triple inoculation. At this point the second triple inoculation was given. The curve continues its rise, showing no break in continuity (this may be an artefact due to the fact that no examination was made for seven days after the second triple inoculation) and reaches its maximum on the eighteenth day after the second triple inoculation. In common with the majority of the other curves, the *B* is the last to attain its maximum. A fall in titer (56 per cent.) is recorded on the thirty-seventh day after the first triple inoculation (twentieth day after the second triple inoculation). On the thirty-sixth day after the second triple inoculation a rise in titer (30 per cent.) similar to that seen in the *T* and *A* curves on the same days, is noted. A fall (33 per cent.) then takes place (forty-sixth day after the second inoculation) similar to that noted for the *A* titer for the same days.

W. C. D.—(Group 11, Curve 23.) Twenty months after the last *T* inoculation the *number of typhoid standard agglutinin* units had fallen to 7. The *T* titer had fallen to 4 standard agglutinin units when examined five months later. At this point (that is, twenty-fifth month after the last *T* inoculation) the first triple inoculation was given. The same quick rise as has been described above (Curves 19, 20 and 22) in men previously inoculated with *T* is again well brought out in this curve, for on the sixth day after the first triple inoculation there is a rise of over 180 per cent. The *T* titer reaches its maximum on the eighteenth day. At this point the second triple inoculation is given.

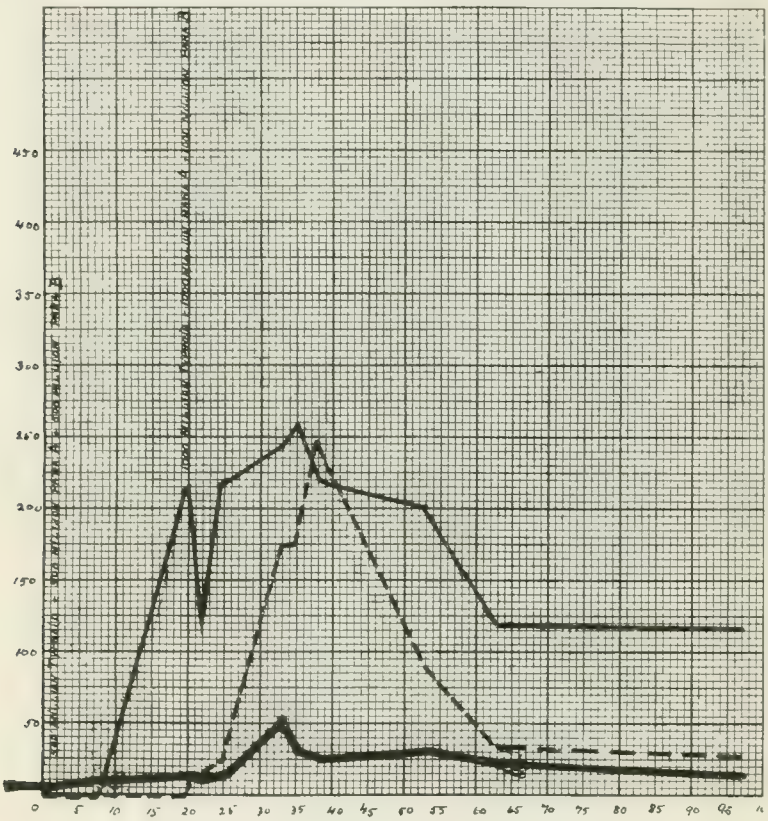
TABLE 26.—DATA FROM WHICH CURVE 23 WAS PLOTTED

Day of Experiment	Standard Agglutinin Units		
	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B
1	4.3*	0	0
2	Inoculation, 0.5 c.c. A A B = 500 million T + 500 million A + 500 million B		
8	10.0	1.43	0
20	14.0	214.0	2.85
20	Inoculation, 1.0 c.c. T A B = 1,000 million T + 1,000 million A + 1,000 million B		
22	13.0	118.0	17.8
25	14.0	219.0	25.0
34	52.0	243.0	173.5
36	29.2	260.0	175.7
39	25.5	218.0	244.0
54	32.4	200.0	89.0
64	21.5	114.2	32.0
67	14.8	114.2	29.0

* Immunized with three doses of B. typhosus vaccine (first, 500 million; second, 1,000 million; third, 1,000 million) twenty-five months previous to present experiment.

The titer has fallen, that is (negative phase on the second day following this last inoculation), but on the third day the new rise is recorded and on the fourteenth day the maximum is reached. A sharp fall (42 per cent.) is recorded by the sixteenth day. From this point the fall in titer is but gradual, showing that the *T* curve has reached its point of equilibrium.

The paratyphoid A agglutinins show a very slight rise on the sixth day following the first triple inoculation. This rise reaches its maximum on the eighteenth day. At this point the second triple inoculation was given. A fall of 45 per cent. (that is, negative phase) is recorded two days later and on the



Curve 23

fifth day after the second triple inoculation the new rise occurs, which attains its maximum on the sixteenth day. From this point the curve falls, reaching its point of equilibrium on the forty-fourth day after the second triple inoculation. When next examined on the seventy-seventh day (after the second triple inoculation) the *A* titer showed no change.

The paratyphoid B agglutinins showed a very slight rise on the eighteenth day after the first triple inoculation. At this point the second triple inoculation was given. The curve continues its rise to a maximum on the nineteenth day after the second triple inoculation. From this point the curve falls, reaching its point of equilibrium on the forty-fourth day after the second inoculation. The fall noted on the seventy-seventh day was but slight (10 per cent.).

DISCUSSION OF RESULTS

In discussing the results obtained in the foreging experiments it will be of advantage to consider, first, the meaning of the curves obtained in rabbits, together with certain features which are common to both series of curves. The curves from man may then be analyzed in the light of the facts observed and the conclusions drawn from the animal experiments.

It may, however, be asserted at the outset that both sets of curves exhibit certain points with equal clearness. These common general features are the following:

1. The general type of the reaction to inoculation is the same throughout both series of curves, the second inoculation with any given vaccine almost invariably raising the agglutinin titer to a much higher level than that reached after the first inoculation. And it will be noted that even where the reaction to the first inoculation is somewhat feeble, a good immunity may be expected after reinoculation.

2. Individual idiosyncracy plays an important part in the degree of immunity resulting from inoculations made with equal doses of vaccine in different animals of the same species, whatever the particular vaccine employed. It also plays a part in determining in mixed inoculation (mixed vaccine) which of the constituent micro-organisms will produce the best reaction.

3. Species also clearly plays a part in this connection. For it will be noted that while the reaction to paratyphoid B is practically always lowest in the rabbit curves, this is not by any means the case in man.

4. The immediate effect of any second immunizing inoculation depends to a considerable extent on the precise period in the curve of the first inoculation at which it is introduced. Thus, if the second inoculation is given before the rise due to the first inoculation has reached its maximum, the curve may show no break in continuity, but continues to rise to the maximum resulting from the second inoculation. Whether or not a distinct maximum for each rise is seen appears to depend on various factors, one of which is the interval between the two inoculations; and one of three conditions may result: (1) the maximum of the first rise may be attained before the second inoculation; (2) the maximum of the first rise may be attained after the second inoculation, in which case a fall will be recorded before the second rise commences; (3) there may, as already stated, be no break in the continuity of the curve, and but one maximum may be noted, which may perhaps represent that of the second rise, or perhaps that of the two rises together.

5. These curves have been plotted directly from the actual readings and no attempt has been made to remove any gross irregularities in

TABLE 27.—SUMMARY OF THE—

Title of Experiment	Bacilli	First Inoculation			Second Inoculation			
		Doses*	First Indication of Rise	Maximum Rise	Interval, Days	Doses	First Indication of Rise	Maximum Rise
Group I Curve 1 Rabbit 1	T	1,000	3	9	11	2,000	3	5
	A	500	2	6	11	1,000	2	5
	B	500	3	6	11	1,000	3	10
Group I Curve 2 Rabbit 2	T	1,000	3	7	15	2,000	1	6
	A	500	3	7	15	1,000	2	5
	B	500	4	7	15	1,000	3	4
Group II Curve 3 Rabbit 3	T	None	0	0	.	None	0	0
	A	500	2	8	11	1,000	3	5
	B	500	3	8	11	1,000	3	4
Group II Curve 4 Rabbit 4	T	None	0	0	..	None	0	0
	A	500	3	5	11	1,000	1	4
	B	500	3	6	11	1,000	1	4
Group III Curve 5 Rabbit 5	T	1,000	3	11	11	2,000	4	11
	A	None	5	11	..	None	0	0
	B	None	4	5	..	None	1	8
Group III Curve 6 Rabbit 6	T	1,000	3	9	11	2,000	....	....
	A	None	0	0	..	None	..	....
	B	None	0	0	..	None	...	....
Graup IV Curve 7 Rabbit 7	T	1,000	3	9(12)	9	2,000	1 or 4	13
	A	500	2	8	9	1,000	1	9 or 12
	B	500	3	9	9	1,000	1	13
Graup IV Curve 8 Rabbit 8	T	1,000	0	0	9	2,000	3	18
	A	500	0	0	9	1,000	3	10
	B	500	0	0	9	1,000	3	10
Group V Curve 9 Rabbit 9	T	500	4	10	....	....	....	....
	A	250	2	2	....	....	...	....
	B	250	...	.	....	....	....	....
Group V Curve 10 Rabbit 10	T	500	7	12	....	.....	...	....
	A	250	....	....	...	.....	....	....
	B	250	17	34	....	.....	....	....

* Numbers in columns of doses refer to numbers of millions of bacilli injected.

—Experiments on Rabbits

Third Inoculation				Fourth Inoculation			
Interval, Days	Doses	First Indication of Rise	Maximum Rise	Interval, Days	Doses	First Indication of Rise	Maximum Rise
55	1,000	4	5	10	2,000	3	6
	None	2	2 and 8		None	0	0
	None	2	9		None	2	4
55	1,000	5	6	10	2,000	5	5
	None	1	2		None	2	3
	None	0	0		None	2	5
	None	0	0		None	5	8
55	500	2	4	10	500	3	7
55	500	3	4	10	500	3	5

TABLE 28.—SUMMARY OF RESULTS OF—

Title of Experiment	Bacilli	First Inoculation			Second Inoculation			
		Doses*	First Indication of Rise	Maximum Rise	Interval, Days	Doses	First Indication of Rise	Maximum Rise
Group VI Curve 11 W. G.	T	500	7	9	9	1,000	5	7
	A	250	7	9	9	500	5	14
	B	250	9	9	9	500	5	14
Group VI Curve 12 J. G. J.	T	500	7	15	15	1,000	7	7
	A	250	7	15	15	500	7	7
	B	250	15	15	15	500	7	7
Group VII Curve 13 R. F. D. R.	T	None	0	0	..	None	0	0
	A	250	7	10 or 14	10	500	9	9
	B	250	7	10 or 14	10	500	4 or 14	16
Group VII Curve 14 H. W. T	T	None	0	0	..	None	0	0
	A	250	7	10 or 18	10	500	16	16
	B	250	10	10 or 18	10	500	16	16
Group VIII Curve 15 T. P.	T	500	7	10	10	1,000	7	7 or 16
	A	None	0	0	..	None	0	0
	B	None	0	0	..	None	0	0
Group VIII Curve 16 E. A. W.	T	500	7	10 or 14	10	1,000	4 or 14	14
	A	None	7	10	..	None	....	....
	B	None	7	10	..	None	9	9
Group IX Curve 17 W. C. C.	T	500	8	14	19	1,000	38	38
	A	250	8	14	19	500	38	38
	B	250	8	19	19	500	38	38
Group IX Curve 18 F. H. H.	T	500	18	18	21	1,000	23	23
	A	250	18	18	21	500	10	10
	B	250	18	21	21	500	10	10

* Refer to footnote to Table 27.

—Experiments on Men

Third Inoculation				Fourth Inoculation			
Interval, Days	Doses	First Indication of Rise	Maximum Rise	Interval, Days	Doses	First Indication of Rise	Maximum Rise
.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....	.....
23	500	.....	.....	9	1,000	3	12
.....	None	2	2	.....	None	12	12
.....	None	2	2	.....	None	12	12
25	500	10	10	10	1,000	2	13
.....	None	3	3	.....	None	2	2
.....	None	10	10	.....	None	.....	.....
.....	None	.....	.....	.....	None	3	.....
23	250	5	3 or 12	9	500	3 or 14	3 or 14
23	250	.....	.....	9	500	14	14
.....	None	.....	.....	.....	None	.....	.....
25	250	10	10	10	500	2	12
25	250	10	10	10	500	2	12
.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....	.....

TABLE 29.—Summary of Experiments on Men

Title of Experiment	Bacilli	Previous Typhoid Immunization; Doses at Weekly Intervals	First Triple Inoculation				Second Triple Inoculation			
			Interval, Mo.	Dose	First Indication of Rise	Maximum Rise	Interval, Mo.	Dose	First Indication of Rise	Maximum Rise
Group X Curve 19 J. W.	T	(1) 500 (2) 1,000	10	500	5	19	19	1,000	14	14
	A	None	10	250	14	19	19	500	14	14
	B	None	10	250	14	19	19	500	14	14
Group X Curve 20 E. H. N.	T	(1) 500 (2) 1,000 (3) 1,000	32	500	3	40	40	1,000	17	17
	A	None	32	250	..	40	40	500	1	17
	B	None	32	250	..	40	40	500	1	17
Group X Curve 21 E. F. H.	T	(1) 500 (2) 1,000 (3) 1,000	22	500	..	..	9	1,000	5	5
	A	None	22	250	9	9	9	500	5	12
	B	None	22	250	9	9	9	500	5	5
Group XI Curve 22 A. D. G.	T	(1) 1,000	14	500	6	16	16	1,000	7	7
	A	None	14	500	6	16	16	1,000	7	16
	B	None	14	500	16	16	16	1,000	7	18
Group XI Curve 23 C. D.	T	(1) 500 (2) 1,000 (3) 1,000	25	500	6	18	18	1,000	5	14
	A	None	25	500	6	18	18	1,000	5	16
	B	None	25	500	18	18	18	1,000	2	19

accordance with preconceived ideas as to the form of the finished curves. Further experiments are necessary before it is possible to decide whether some of these gross irregularities are due to inaccuracies of technic, or whether they represent the correct amounts of free agglutinins in the circulation at the time of examination.

The majority of these irregularities fall into one class, namely, quick secondary rises or rebounds during an otherwise rapidly falling curve (usually thirteen or fourteen days after inoculation). If this sudden secondary rise for from twenty-four to forty-eight hours in a falling curve is not due to faulty technic, it might be explained as the irregular reaction of an exhausted agglutinogenic mechanism. The remainder of the gross irregularities occur as sudden, temporary secondary falls during a rising curve. Possibly the agglutinogenic mechanism which is responding to the stimulation of the vaccine by a rapid production of free agglutinins into the peripheral circulation is tem-

porarily exhausted and cannot continue its rapid production of agglutinins until after an interval of comparative recuperation or until the mechanism has become compensated or accommodated to this unaccustomed stimulation.

As I said before, further experimentation alone will show whether these gross irregularities correctly represent the amounts of free circulating agglutinins at the time of examination, or whether they are due to inaccuracies of technic.

The Curves from Rabbits.—1. From the Rabbit Curves 3, 4, 5 and 6, it is seen that an animal already immunized to one or more bacilli responds to subsequent inoculations of one or more different bacilli in two ways: First, it produces specific agglutinins for the bacilli last injected, and second, it shows a temporary new increase in the agglutinin titer for the bacilli injected first. Such temporary rises of the original agglutinins exhibit two different types in different cases. There may be (1) a sharp "kick-up" following almost immediately on heterologous inoculation (also seen in Curve 13 [human]), or (2) a later rise whose apex corresponds with the maximum of the specific curve of the later immunization. The first type is apparently a rapid nonspecific response to the injection of a toxic substance, for an exactly similar reaction has been shown to occur to other forms of chemical or physical irritation (that is, bleeding,[31] injection of any toxic fluid, etc.). As I shall point out later (in connection with the Human Curve 13), this sudden increase in agglutinin may perhaps be related to the extensive destruction of leukocytes which Bull[32] states to be caused by inoculations.

The latter type of rise may be explained as due to a "sympathetic" increase of activity of the whole antibody producing mechanism at the time when the new specific mechanism reaches its maximum of activity.

This "sympathetic" response is also frequently well marked in a somewhat different connection. Thus, it may be seen, for instance, in Curve 1, that the typhoid and paratyphoid A curves, following triple inoculation, attain their maxima and commence their fall while the paratyphoid B titer is still rising. But as the paratyphoid B curve approaches and attains its maximum, the fall of the typhoid and paratyphoid B curves is arrested, so that a plateau results which persists in each case until after the paratyphoid B titer has passed its maximum.

2. By comparing the Curves 3, 4, 5 and 6 with Curves 1, 2, 7 and 8, in which typhoid, paratyphoid A and paratyphoid B were injected simultaneously, it is seen that a given dose of a bacillus when injected *simultaneously* with other bacilli gives rise to as good an immunity

31. Schroeder, K.: Thesis, Copenhagen, 1906.
32. Bull, C. G.: Jour. Exper. Med., 1916, **23,** 419.

reaction as when it is injected alone in the same dosage. This point is one of great practical importance in its bearing on prophylactic inoculation against the enteric fevers (typhoid, paratyphoid A, and paratyphoid B).

3. In the Curves 1-8, the commencement of the rise of the agglutinins of the organism first injected shows marked regularity, for in 12 out of 17 instances the rise commenced on the third day, and of the other 5 cases, in 2 it occurred on the second day, in 2 on the fourth and in 1 on the fifth day after inoculation.[33]

4. The maxima of the rises in the rabbits' curves due to the first inoculations do not show the same regularity, as they range from the fifth to the eleventh day, the average being 7.7 days.

This fact, that is, that the first rise reaches its maximum about the seventh day, is of practical importance, as it indicates the optimum time to give a second inoculation. For it is seen that in curves in which the second inoculation is given before the curve from the previous inoculation has commenced to fall, a greater amount of agglutinins is produced.

5. For inoculations other than the first there is not the same regularity seen in regard to the commencement of the rise or the attainment of the maximum, though the response is usually more rapid than on the first occasion.

6. With the exception of Curves 1, 2, 3 and 5 in rabbits, and 12, 16 and 20 in man, the paratyphoid B agglutinins commence their rise and attain their maximum later than the typhoid and paratyphoid A agglutinins.

7. It is evident from the study of Curves 9 and 10, and from a comparison of them with any of the others, that giving a rabbit an inoculation with this dose, that is, 500 million typhoid and 250 million paratyphoid A and 250 million paratyphoid B, produces a much smaller amount of agglutinins than giving a man the same dose; in other words, the mechanism for antibody production in man is very much more sensitive to those organisms than that of a rabbit, and to get similar effects we must increase the dosage for rabbits.

This dose of 500 million typhoid and 250 million paratyphoid A and 250 million paratyphoid B is evidently less than the dose required to give a good immunity reaction in rabbits, while a dose of 1,000 million typhoid and 500 million paratyphoid A and 500 million para-

33. It must be remembered in this connection that owing to the exigencies of the case, inoculations could not always be made, or blood withdrawn at a constant hour of the day. This was usually done. But it is possible that variations in the time of commencement of the rise, not exceeding one day, might be due to early or late inoculation or bleeding as the case may be.

typhoid B (as in Curves 1-8) appears sufficient. Castellani has shown in rabbits that increasing the dose above this last named strength does not appreciably increase the amount of the agglutinins produced. In men in Curves 24 and 25 I found that increasing the proportions of paratyphoid A and paratyphoid B appeared to increase the amount of agglutinins produced for these organisms (in comparison with typhoid titer), but this may have been due to individual idiosyncrasy.

The Curves from Man.—1. Curves 13, 14, 15 and 16 in the men (as does Curve 3 in rabbits) show that the immunity reaction to the later organism is less intense than that to the first (except for paratyphoid A in curve 16) and may actually fail to reach the level to which the first agglutinins have fallen (B, Curve 15).

Curves 13 and 14 also show that the stimulus of the second immunization causes a definite rise in the agglutinins of the first organisms. In Curve 13 the phenomena occurs twice:

First within forty-eight hours of the first typhoid inoculation there is a sharp rise of the paratyphoid A and paratyphoid B curves, probably due to the general stimulation of the inoculation already referred to in the discussion of the results in rabbits. Since Bull[32] declares that the inoculations cause extensive destruction of leukocytes, it may be suggested that the two phenomena bear a direct relationship to one another and that this leukocytic disintegration liberates the agglutinins, as has been shown in vitro.[34]

Secondly, in Curves 13, 14 and 15 a rise in the agglutinins of the first organisms is seen at or about the point at which the maximum of the agglutinins of the later organisms has occurred. This second type of rise is of great importance in interpreting the results of clinical agglutination tests in inoculated individuals. For instance, in a typhoid inoculated person who acquires a paratyphoid infection, the rise in the typhoid titer which has been described as occurring during the course of the active infection is a rise of this second type. The first type of rise (Curve 13) corresponds very closely with the phenomenon seen in the curves of inoculated individuals who have been subjected to a rather intense nonspecific stimulus such as a simple bleeding or the inoculation of an entirely different organism.[31]

2. In Curve 16 a plateau is seen in the curve of the organism first inoculated (that is, typhoid) to follow immediately on the first inoculation of the later organisms, that is, paratyphoid A and paratyphoid B. I should be inclined to attribute this to the stimulus of this inoculation if it were not for the fact that such plateaus are found to occur in this and in other falling curves at points where no inoculations were given

34. See Footnotes 19, 20 and 21.

(*vide supra*). No rise in the typhoid titer is seen at the maximum of the paratyphoid A or paratyphoid B curves, although its apparent absence may be due to the length of the interval between examinations. Since it must always be remembered in curves plotted from observations made at intervals longer than twenty-four hours, sharp rises and falls may at times escape detection.

3. By comparing Curves 13, 14, 15 and 16 with curves 11 and 12, in which typhoid, paratyphoid A and paratyphoid B were injected simultaneously, it is evident that, as in rabbits, so also in men, the same quantities of bacilli when injected *simultaneously* with other bacilli give for *each* organism *as good* and usually a *greater* immunity reaction than if it had been *injected alone* (and as a first inoculation).

4. In Curves 19, 20, 22 and 23 in which typhoid inoculation had been given from one to three years previously, it was found that when the triple vaccine was injected the typhoid titer rose earlier than in individuals who had not received typhoid injections previously.

From this quick response to reinoculation by an immunized individual it may well be deduced that one of the ways in which prophylactic inoculation confers immunity is by habituating the protective mechanism to the formation of particular antibodies so that it remains in a state of readiness which enables it to react with a much shorter latent period to the invasion of the specific organisms and either to prevent them gaining a foothold or to abort the infection in an early stage.

5. *Negative Phase.*—In certain curves, 14, 15, 16, 18, 19, 20 and 23, in the men, we see (as in Curves 1-6 in rabbits) a short, sharp, unexpected fall within forty-eight hours after any inoculation other than the first. This is best interpreted as a negative phase. In some cases (that is, in falling curves) this fall might be explained as the continuation of the natural fall, but in other cases, that is, those in which the curve immediately preceding this sharp fall was practically level for six months (as in Curve 19) there *appears* no interpretation other than that of Wright's[35] negative phase. This would *appear* to be in contradiction to the results of Bull.[32]

CONCLUSIONS

From the foregoing discussion of the results obtained in these experiments the following conclusions bearing on the practical problem of prophylactic inoculation in man against the typhoid-paratyphoid group of organisms stand out as possessing paramount importance:

1. When a mixed vaccine is used the immunity obtained for each of its constituent bacilli is at least as good as, and very often greater

35. Wright, A. E.: Brit. Med. Jour., 1903, **1,** 1069. Von Wassermann, A., and Summerfield, P.: Med. Klin., 1915, **11,** 1307.

than, that obtained against any one of these organisms when it is employed alone in the same dosage for a first immunization.

2. When single vaccines are employed in succession and the immunizations are carried out independently, the response is greatest to that vaccine which is introduced first. To the later immunizations with other micro-organisms the specific response is almost always less intense. It has associated with it, however, as a secondary result the production of a new rise of variable extent in the agglutinin titer of the serum of the bacillus of the first immunization.

ADDITIONAL REFERENCES

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Madsen and Jorgensen, Festskrift ved Indu. af Statans Seruminst., Copenhagen, 1902.

A STUDY OF THE METABOLISM OF ASTHMA*

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The effects of asthma on the anabolism and katabolism of the human body should be considered from different points of view. The causative factor (for example, anaphylaxis, etc.) may induce certain pathochemical changes which lead to asthma as one of the results, and these pathochemical changes are the disturbing factors in the metabolism of these patients, or, again, the syndrome, asthma, may affect the metabolism of the patient by (for instance) depriving the blood of oxygen, or by affecting the nervous system, circulatory system, etc. When, therefore, results are reported of the metabolism findings in asthmatic individuals, discrimination should be used as to which factor is to be held responsible for these deviations from the normal chemical balance of the body.

Before discussing the experiments that we have performed in our study of this disease, we wish to review the literature that may be pertinent to this subject. We have found no report of a complete metabolism study of patients suffering from asthma. The effect of dyspnea on metabolism has, however, been investigated.

Senator[1] has found that moderate respiratory impediment affects but little the nitrogen katabolism, sometimes augmenting it slightly, whereas if the dyspnea becomes very great, the increase of the nitrogen excretion is marked and may last several days after the disappearance of the dyspnea (Fraenkel,[2] Fleischer and Penzoldt,[3] Fraenkel and Geppert,[4] Klemperer,[5] Praussnitz,[6] Araki[7]).

Colosanti is the only observer who comes to the opposite conclusion, and his reputation is such that his work cannot be slighted. Colosanti and Palamenti obstructed the breathing by chemical and by mechanical means, and found that the percentages of urea and nitrogen in the urine were both subnormal as long as the obstruction was main-

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1. Senator: Arch. f. path. Anat. u. Physiol., 1868, **42,** 1.
2. Frankel: Arch. f. path. Anat. u. Physiol., 1876, **57,** 273.
3. Fleischer and Penzoldt: Arch. f. path. Anat. u. Physiol., 1882, **78,** 210.
4. Fraenkel and Geppert: Ueber die Wirkungen der verdunnten Luft auf den Organ, 1883, p. 78.
5. Klemperer: Ztschr. f. klin. Med., 1889, **16,** 584.
6. Praussnitz: Sitzungsb. d. Gesellsch. f. Morphol. u. Physiol. in München., 1890, **5,** 70.
7. Araki: Ztschr. f. physiol. Chem., 1891, **15,** 335.
8. Colosanti and Palamanti: Maly's Jahresb. u. d. Fortschr. d. Thierchem., 1894, **24,** 466.

tained, rising again when the impediment was removed. They also say that the secretion of urine ceased during dyspnea.

Matthes[9] writes: "One must hesitate before accepting unqualifiedly their conclusions that the lessened supply of oxygen diminished the activity of the regressive metamorphoses of the organism."

We shall discuss the Colosanti results later.

It has been generally accepted by the German school that there is a breaking down of protein in dyspnea. Whether this is due to a breaking down of the body cells due to lack of oxygen (a theory suggested by Fränkel), or whether (as Klemperer asserts) the increased protein katabolism is due to a poison produced by the dyspnea, or whether (according to Praussnitz) the primary effect of the dyspnea is to break down the nonnitrogenous substances in the body, and only secondarily to augment the protein decomposition—is a much mooted point.

Saccone[10] found that the restriction of respiration in a dog by the application of a Sayre corset caused an increased elimination of urinary phosphorus, which became normal only after two days.

It has been found by a number of observers that when tissue oxidation is lessened, due to dyspnea, unoxidized products may be eliminated in the urine, as, for example, lactic acid. Senator,[1] for instance, found glucose in the urine of dogs with dyspnea, and Dastre[11] found a hyperglycemia in similar conditions. It was proved by Hoppe-Seyler[12] that the lactic acid excreted under these circumstances was paralactic acid; that is, ethylidene lactic acid.

Dyspnea may be induced by vagus paralysis. But it has been found by Rauber and Voit[13] that the oxygen absorption and the carbon dioxid elimination were not changed in experimental section of both vagi. Von Maar,[14] however, reported different results:

> The absorption of oxygen increases considerably, and generally is doubled, in the lung whose vagus is cut, and it falls almost as much in the other lung. The excretion of carbon dioxid was affected in the same sense as the absorption of oxygen, but to a far less extent. Von Maar found that as soon as the other vagus was cut, the breathing of the two lungs became equalized. He exposed and scrutinized the lung during one experiment, and could see no change in the amount of blood that it contained, thus making it plain that the circulation had nothing to do with the changes observed. On the other hand, by compressing the left pulmonary artery, he did directly disturb the circulation through the lungs (Matthes[15]).

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9. Matthes, M., in C. von Noorden's "Metabolism and Practical Medicine," 1907, **2,** 331.
10. Saccone: Ann. di med. nav., 1907, **13,** (1), 573.
11. Dastre: De la Glycemie asphysique, Thèse de Paris, 1879.
12. Hoppe-Seyler: Ztschr. f. physiol. Chem., 1895, **20,** 365.
13. Rauber and Voit: Sitzungsb. d. k. Akad. d. Wssensch., zu. München, 1868.
14. Von Maar: Skand. Arch. f. Physiol., 1902, 229.
15. Matthes: von Noorden: Metabolism and Practical Medicine, 1907, **2,** 304.

Case 1.—*History.*—A married woman, aged 40, developed a severe attack of asthma when in midocean seven years previously, and continued to be afflicted in varying degrees of severity and almost without interruption until the present report. One maternal aunt was an asthmatic. As a child the patient had one or two attacks of oppressed breathing. History and family history are otherwise negative in so far as they have a bearing on the asthmatic state. Her condition at the time of the examination showed a normal blood pressure, and gave normal urinary findings on routine examination. There was a profuse expectoration of mucopus containing a great variety of bacteria, and there was considerable mucus in the stool. Roentgen-ray examination of the lungs had already shown an absence of any tuberculous lesion, but disclosed the fact that the larger bronchial tube walls were much hypertrophied—a result no doubt of the long continued effort at forced breathing.

Preliminary Laboratory Examinations.—The urine was light, amber, specific gravity 1.018, acid, containing no albumin, glucose or the acetone derivatives, showing a trace of indican. Microscopically, many squamous epithelial cells derived from the vulva were present.

Examination of the blood was negative.

The feces were yellow in color, of semisolid consistence, containing no blood, but rather excessive quantities of mucus which was microscopically negative.

Bacteriologic examination of the sputum showed the presence of staphylococcus, streptococcus, and *Micrococcus catarrhalis.*

The Wassermann test was negative (Dr. Bronfenbrenner).

Method of Procedure.—The patient was put on a Folin diet, which consists of:

Whole milk, 500 c.c.
Cream (18-22 per cent. fat), 300 c.c.
Eggs (white and yolk), 450 gm.
Horlick's malted milk, 200 gm.
Sugar, 20 gm.
Sodium chlorid, 6 gm.
Water enough to make the whole up to 2 liters.

"The ingredients combine into a liquid mixture containing 119 gm. protein, and approximately 148 gm. fat and 225 gm. carbohydrates." (Folin.)

The patient was kept on this diet for three days. The twenty-four-hour urine collections were preserved with thymol. The daily intestinal evacuations were marked off by a capsule of carmin (0.3 gm.).

The following methods were used for the analyses of the urine and feces: The nitrogen was estimated according to Kjeldahl, and the total sulphur by the Benedict[16] method; total and ethereal sulphates, by the Folin[17] method; the inorganic sulphates were computed by subtracting the ethereal sulphates from the total sulphates; the "neutral" sulphur was computed by subtracting the total sulphate sulphur from the total sulphur. Urea was estimated by Benedict's[18] method, ammonia and creatinin by Folin's[19] methods, uric acid by the Folin-Shaffer[20] method, purin bases by the Kruger-Schmidt[21] method, phosphorus by Neumann's[22] method, calcium and magnesium by McCrudden's[23] method.

16. Benedict: Jour. Biol. Chem., 1909, **6,** 363.
17. Folin: Am. Jour. Physiol., 1905, **13,** 51.
18. Benedict: Jour. Biol. Chem., 1911, **8,** 455.
19. Folin: Am. Jour. Physiol., 1903, **8,** 330.
20. Folin and Shaffer: Ztschr. f. physiol. Chem., 1901, **32,** 552.
21. Kruger and Schmidt: See Hawk, Practical Physiol. Chem., Ed. 5, 1916, 513.
22. Neumann: Ztschr. f. physiol. Chem., 1904, **43,** 45.
23. McCrudden: Jour. Biol. Chem., 1911, **10,** 187.

METABOLISM STUDIES

Study of the Nitrogen Metabolism.—The patient took in daily an average of 17.5 gm. nitrogen in her food. In the urine she voided daily an average of 11.4 gm. nitrogen, and in her feces, an average of 2.2 gm. nitrogen. There was thus left a positive balance of 3.9 gm. Nitrogen representing 33.15 gm. protein.

The nitrogen partition of the urine shows the following: The percentage excretion of urea, ammonia, and uric acid nitrogen is normal. There is a slight increase in the elimination of the creatinin and amino-acid nitrogen. The data for the nitrogen partitions are represented in Table 1.

Study of the Sulphur Metabolism.—The patient took daily in her food an average of 3.2 gm. sulphur trioxid (SO_3) and voided in the urine daily an average of 2.4 gm. sulphur trioxid, and in the feces 0.93 gm., causing a negative balance of 0.13 gm. It thus seems that in this case the katabolism of the sulphur portion of the molecule does not go hand in hand with the nitrogen katabolism, for, whereas there was a positive average balance of 3.9 gm. nitrogen, the sulphur shows a loss. The sulphur partition in the urine is very interesting. There is an increase in the nonoxidized sulphur fraction (so-called "neutral sulphur"). This would be in harmony with the findings of Reale and Boeri,[24] who observed that by inducing dyspnea in dogs by compression of the chest, there was a marked increase in the "neutral" sulphur fraction of the urine — even as high as 37.5 per cent. of the total sulphur.

The ethereal sulphates were not increased, showing that there was not present to any extent an intestinal putrefactive condition. Von Noorden[25] found, in general, that there was no deviation from the normal in the limination of the conjugated sulphates in the urine by emphysematous subjects.

Since one of us is interested in the volatile sulphids eliminated in the urine, we determined that fraction in the urine was found that from 2 to 3 per cent. of the total sulphur was volatile sulphid. We made no attempt to identify which of the volatile sulphids were present. It would be interesting to analyze such urine for hydrogen sulphid, mercaptan, ethylsulphid, etc.

The ratio of nitrogen to sulphur was on the average of 11.5 : 1.

The data of the sulphur partition are given in Table 2.

Study of the Mineral Metabolism. — As will be seen from the accompanying data on Table 3, there was nothing strikingly abnormal

24. Reale and Boeri: Wien. med. Wchnschr., 1895.
25. Von Noorden: See Matthes, Footnote 15.

TABLE 1.—Nitrogen Partition—

Day	Volume Urine, C.c.	Nitrogen Gm.	Urea N		Ammonia N	
			Per Cent. Total N	Gm.	Per Cent. Total N	Gm.
1	1,070	12.3	82.7	10.1721	2.5	0.3074
2	760	10.4	80.5	8.373	2.2	0.2288
3	890	11.7	80.2	9.385	3.9	0.4563
Average	906	11.4	81.1	9.2455	2.8	0.3192

TABLE 2.—Sulphur Partition of Urine, Case 1

Day	Total S as SO_3, Gm.	Inorganic SO_3		Ethereal SO_3		Neutral S as SO_3			N:S Ratio
		Per Cent. Total SO_3	Gm.	Per Cent. Total SO_3	Gm.	Per Cent. Total SO_3	Gm.	Volatile S Portion, per Cent. of Total SO_3	
1	2.7	68.8	1.8576	12.8	0.3456	18.4	0.4968	2.4	11.3:1
2	2.1	67.4	1.4254	14.9	0.3129	17.7	0.3727	2.35	12.2:1
3	2.6	66.7	1.7342	14.2	0.3692	19.1	0.4986	2.97	11.2:1
Aver.	2.4	67.6	1.6224	13.9	0.3336	18.4	0.4416	2.57	11.5:1

TABLE 3.—Mineral Excretion in the Urine and Feces, Case 1

Day	Phosphorus Pentoxid		Calcium Oxid		Magnesium Oxid		Chlorin in Urine, Gm.
	Urine, Gm.	Feces, Gm.	Urine, Gm.	Feces, Gm.	Urine, Gm.	Feces, Gm.	
1	2.9	1.2	0.6	1.61	0.92	0.57	5.7
2	3.1	0.8	0.67	1.59	0.87	0.32	5.2
3	2.7	1.9	0.72	1.82	0.91	0.42	6.3
Average	2.9	1.3	0.66	1.67	0.9	0.43	5.7
Total	4.2		2.33		1.33		

in the elimination of phosphorus, calcium and magnesium in the urine and feces. There was an average daily positive balance of 0.9 gm. phosphorus pentoxid (P_2O_5), 0.36 gm. calcium oxid (CaO), 0.12 gm. magnesium oxid (MgO). The French school of physicians have described phenomena of marked demineralization, that is, loss of calcium oxid, phosphorus pentoxid and magnesium oxid in pulmonary

—OF URINE. CASE 1

Amino-Acid N		Uric Acid N		Purin Base N		Creatinin N		Rest N
Per Cent. Total N	Gm.	Per Cent. Total N	Gm.	Per Cent. Total N	Gm.	Per Cent. Total N	Gm.	Per Cent. Total N
2.1	0.2586	2.7	0.3321	2.2	0.2706	5.7	0.7011	0.2
3.7	0.3848	1.8	0.1871	2.1	0.2184	6.1	0.6344	3.3
4.3	0.5031	2.8	0.3276	1.9	0.2223	5.8	0.6786	1.1
3.3	0.3762	2.4	0.2736	2.06	0.2348	5.6	0.6612	1.5

TABLE 4.—BALANCE SHEET. CASE 1

	Nitrogen		Sulphur Trioxid		Phosphorus Pentoxid		Calcium Oxid		Magnesium Oxid	
	Feces, Gm.	Urine, Gm.	Feces, Gm.	Urine, Gm.	Feces, Gm.	Urine, Gm.	Feces, Gm.	Urine, Gm.	Feces, Gm.	Urine, Gm.
Aver. daily intake...	17.5		3.2		5.1		2.7		1.4	
Output first day.....	12.3	2.2	2.7	0.8	2.9	1.2	0.6	1.61	0.92	0.57
Total.....	14.5		3.5		4.1		2.21		1.49	
Output second day.	10.4	2.7	2.1	0.7	3.1	0.8	0.97	1.3	0.87	0.32
Total.....	13.1		2.8		3.9		2.26		1.19	
Output third day...	11.7	1.8	2.6	1.3	2.7	1.9	0.72	1.82	0.91	0.42
Total.....	13.5		3.9		4.6		2.54		1.33	
Average output.....	11.4	2.2	2.4	0.93	2.9	1.3	0.66	1.67	0.9	0.43
Total...	13.6		3.33		4.2		2.33		1.33	
Total intake, three days.....	52.5		9.6		15.3		8.10		4.2	
Total output, three days.....	41.1		10.2		12.6		7.01		4.01	
Balance after three days..... ..	−11.4		−0.6		+2.7		+1.09		+0.19	
Average daily balance.....	+3.8		0.2		+0.9		+0.36		+0.12	

phthisis. This patient has no evidence whatever of tuberculosis. As far as we are aware, the mineral metabolism of asthma has never been previously studied.

In Table 4 is given a balance sheet of the intake and output of nitrogen, sulphur trioxid, phosphorus pentoxid, calcium oxid and magnesium oxid. The average intake of the three days is given. The output data are given in their daily quantities.

CASE 2.—*History.*—A young woman, aged 29, married, with a healthy child. Her family history is negative. Her past history shows that when a child she had several attacks of pleurisy and pneumonia. During the past few years she complains of shortness of breath, of occasional typical asthmatic seizures, which pass off after several hours. Her heart and kidneys are normal. A slight degree of emphysema is present.

The urine examination is negative; specific gravity, 1.016. Examination of the feces is negative. The sputum shows many streptococci, pneumococci and pus cells. Negative for tubercle bacilli after guinea-pig inoculation. The blood count shows hemoglobin, 90 per cent.; red blood cells, 4,200,000; white blood cells, 10,200; polynuclears, 62 per cent.; mononuclears, 35 per cent.; eosinophils, 3.0 per cent. The Wassermann test is negative.

This patient was also kept on a Folin diet for three days, and her metabolism was studied on the plan described under Case 1.

Study of the Nitrogen Metabolism.—From the data of Table 8 it will be seen that the patient took in daily an average of 18.8 gm. of

TABLE 5.—URINARY NITROGEN—

Day	Volume Urine, C.c.	Nitrogen	Urea N		Ammonia N	
			Per Cent. Total N	Gm.	Per Cent. Total N	Gm.
1	1,520	14.94	85.5	12.7737	4.7	0.7022
2	1,725	14.82	86.4	12.805	4.1	0.6076
3	1,650	14.35	84.2	12.1827	3.5	0.5022
Average	1,631	14.703	85.3	12.5391	4.1	0.6027

TABLE 6.—URINARY SULPHUR PARTITION, CASE 2

Day	Total S as SO_3, Gm.	Inorganic SO_3		Ethereal SO_3		Neutral S as SO_3			N:S Ratio
		Per Cent. Total SO_3	Gm.	Per Cent. Total SO_3	Gm.	Per Cent. Total SO_3	Gm.	Volatile S Portion, per Cent. of Total SO_3	
1	3.87	52.4	2.0278	29.7	1.1494	17.9	0.6917	2.15	9.9:1
2	3.81	54.1	2.0558	26.8	1.1211	19.1	0.5677	3.22	9.5:1
3	3.72	56.0	2.0832	27.5	0.8230	16.5	0.6138	2.17	9.8:1
Aver.	3.8	54.1	2.0558	28.0	1.0640	17.8	0.6764	2.51	9.7:1

TABLE 7.—MINERAL EXCRETION IN URINE AND FECES, CASE 2

Day	Phosphorus Pentoxid		Calcium Oxid		Magnesium Oxid	
	Urine, Gm.	Feces, Gm.	Urine, Gm.	Feces, Gm.	Urine, Gm.	Feces, Gm.
1	3.21	1.07	0.92	2.2	0.35	0.09
2	3.32	1.12	0.85	2.5	0.32	0.11
3	2.95	1.70	0.94	2.4	0.33	0.12
Average	3.19	1.29	0.903	2.3	0.33	0.106
Total	4.48		3.203		0.436	

nitrogen and excreted daily an average of 14.703 gm. nitrogen in the urine and 2.83 gm. in the feces, showing a positive average balance of 1.267 gm. nitrogen, or 7.918 gm. protein. The nitrogen partition was normal, except, perhaps, that there is a slight deduction in the creatinin excretion. The urea nitrogen, ammonia nitrogen, purin base and uric acid nitrogen and amino-acid nitrogen fractions are normal.

Study of the Sulphur Metabolism.—It will be seen (Table 8) that the patient took in a daily average of 4.785 gm. sulphur trioxid in her

--PARTITION, CASE 2

Amino-Acid N		Uric Acid N		Purin Base N		Creatinin N		Rest N
Per Cent. Total N	Gm.	Per Cent. Total N	Gm.	Per Cent. Total N	Gm.	Per Cent. Total N	Gm.	Per Cent. Total N
1.7	0.2539	2.0	0.2988	2.1	0.3137	2.2	[illegible]	1.8
2.1	0.3112	1.9	0.2816	2.5	0.3705	2.7	0.4001	0.4
1.9	0.2726	17.	0.2439	1.9	0.2726	3.2	0.4582	2.6
1.9	0.2793	1.86	0.2744	2.1	0.3087	2.7	0.3569	1.6

TABLE 8.—BALANCE SHEET, CASE 2

	Nitrogen		Sulphur Trioxid		Phosphorus Pentoxid		Calcium Oxid		Magnesium Oxid		Chlorin in Urine, Gm.
	Urine, Gm.	Feces, Gm.	Urine, Gm.	Feces, Gm.	Urine, Gm.	Feces, Gm.	Urine, Gm.	Feces, Gm.	Urine, Gm.	Feces, Gm.	
Aver. daily intake..	18.8		4.785		4.91		3.25		0.46		6.37
Output first day...	14.94	2.37	3.87	0.65	3.21	1.07	0.92	2.2	0.35	0.09	6.14
Total.....	17.31		4.52		4.28		3.12		0.44		
Output second day.	14.82	2.56	3.81	0.67	3.32	1.12	0.85	2.5	0.32	0.11	6.25
Total.....	17.38		4.48		4.44		3.35		0.43		
Output third day...	14.35	2.74	3.72	0.72	2.95	1.70	0.94	2.4	0.33	0.12	6.03
Total.....	17.09		4.44		4.65		3.34		0.45		
Average output....	14.703	2.83	3.8	0.68	3.19	1.29	0.903	2.3	0.33	0.106	6.14
Total.....	17.533		4.48		4.48		3.203		0.436		
Total intake, three days.....	56.4		14.355		14.73		9.75		1.38		
Total output, three days.....	52.599		13.44		13.44		9.609		1.308		
Balance after three days.....	+3.601		+0.915		+1.29		+0.141		+0.072		
Average daily balance.....	+1.267		+0.305		+0.43		+0.047		+0.024		

food, and that she eliminated a daily average of 3.8 gm. sulphur trioxid in the urine and 0.68 gm. sulphur trioxid in the feces, leaving a daily positive balance of 0.305 gm. sulphur trioxid.

The urinary sulphur partition (Table 6) is interesting. The excretion of ethereal sulphates is increased, the figures being almost twice

the quantities voided in Case 1. It is interesting to note here that Patient 1 was accustomed to make rectal lavages and keep her bowels generally well evacuated. This patient (Case 2) is suffering from some intestinal stasis.

The neutral sulphur fraction is increased also in this patient, showing some condition of suboxidation. The volatile sulphid excretion is 2.51 per cent. of the total sulphur voided in the urine.

The N : S ratio is 9.7 : 1.

The mineral metabolism shows an average daily positive balance of 0.43 gm. phosphorus pentoxid, 0.047 gm. calcium oxid and 0.024 gm. magnesium oxid (Table 8). The excretion of phosphorus pentoxid, calcium oxid and magnesium oxid (Table 7) is normal.

GENERAL DISCUSSION

Asthmatic individuals seem to suffer from a condition of tissue suboxidation. Whether this is due to the lack of oxygen induced by the functional failure of the pulmonary system, or whether the suboxidation is the result of the causative factor of the disease and is, perhaps, the etiologic factor in the production of the spasmodic seizure, cannot, of course, be at the present time decided. If it were possible to study the metabolism of a patient who did not suffer from asthma, but who had the etiologic factors present that may induce asthma, as, for example, an anaphylactic state that is present without the asthma, this point may be cleared up. The neutral sulphur[26] fraction (consisting of the various unoxidized sulphur derivatives, like taurine, taurocarbamic acid, cystin, sulphocyanates, the oxyproteic and uroferric acid, the volatile sulphids, etc.) increase shows this lack of oxidation. This seems to agree with the findings of various observers who noticed a decrease of tissue oxidation in dyspneic animals.

We find also that the creatinin output is low, thus indicating a lessened tissue oxidation, for, according to Folin[27] and others, the creatinin output depends only on the endogenous katabolism of the body.

While we did not notice that there was a lessened excretion of urea in urine, we found that the observation of Colosanti that there was a decrease in tissue breakdown during dyspnea, held true in human beings suffering from asthma. It is not true, however, that secretion of urine stops during the dyspneic attack, for in one case the secretion of urine seemed to be stimulated during the spasm, at least the patient voided urine frequently.

26. Kahn: Urinary Volatile Sulphids. To be published.
27. Folin: Am. Jour. Physiol., 1905, **13,** 45.

CONGLOMERATE TUBERCLE AND COMBINED DEGENERATION OF THE CORD AS COMPLICATIONS OF VISCERAL TUBERCULOSIS *

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I. TUBERCULOSIS OF THE SPINAL CORD

Occurrence and Pathology.—Excluding ordinary tuberculous meningitis and tuberculosis of the meninges due to extension from Pott's disease, tuberculosis of the cord is comparatively uncommon. As a feature of the extremely common disease, tuberculosis, it is decidedly rare, but considered in connection with the relatively rare syndrome of spinal cord tumor, it is fairly common. Thus, among 213 cases of cord tumor collected by Edward Flatau[1] tubercle ranked first among the 58 cases of intramedullary tumor, glioma being second with 14 and sarcoma third with 13. Carl Doerr[2] in his paper of 1911, however, was only able to collect 74 cases, adding only 12 from the literature to the 62 in Schlesinger's[3] monograph of 1898, and two new ones.

Aside from a few cases of acute tuberculous meningomyelitis, practically all cases are instances of tumor-like "solitary," more properly conglomerate tubercle, and usually are due to infection of the interior of the cord by way of the blood stream, or, more rarely, to extension along the lymphatics in cases of meningeal tuberculosis. Doerr says that in three-fourths of all cases of conglomerate tuberculosis of the cord there has been present a tuberculous spinal meningitis which sometimes was the consequence and sometimes the result of the intramedullary tuberculosis. In 72 of the 76 cases the region affected was stated: Cervical 22, thoracic 15, lumbar 32, sacral 3. Contrary to expectation, the cord affection is much less frequently secondary to tuberculosis of the spinal column and meninges than to tuberculosis of the lungs, joints and bones other than the vertebrae. A few authors have asserted that their cases were instances of primary localization of the tubercle bacillus in the cord, but this obviously is improbable in itself and is not considered proved by Doerr.

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* From the Presbyterian Hospital.
* Read before the Chicago Society of Internal Medicine May 28, 1917.

1. Flatau, Edward: Handbuch der Neurologie, 1911, **2**, 641.
2. Doerr, Carl: Arch. f. Psychiat., 1911, **49**, 406.
3. Schlesinger: Beiträge zur Klinik der Bückenmark und Wirbel-Tumoren, Jena, 1898.

Sex and Age Incidence, and Rôle of Trauma.—It is curious that of 54 cases in Doerr's statistics, 46 were in males, 8 in females, and Schlesinger found a similar preponderance of males in all intramedullary tumors, the ratio being 4 to 1. As to age, most of the cases have occurred in the first, third and fourth decades, namely, 15, 14 and 16, respectively, out of 63 cases, the extremes of age being 8 months and 66 years. Trauma to the back seems to be an important factor in determining localization in the cord, and the same is true of severe attacks of acute infectious diseases, especially acute articular rheumatism and scarlet fever.

Symptomatology.—The onset is usually with pain, paresthesias and weakness of one extremity, rapidly spreading to the other side, so the picture of a transverse lesion is produced. Pain usually precedes paralysis, except when the ventral horns are primarily affected. Dissociation of sensation with disproportionate affection of the temperature sense is frequent, but later all forms of sensation are usually affected. Muscular atrophies and vasomotor disturbances are common. Tenderness of the spine is not common but stiffness fairly common. The behavior of the reflexes naturally varies according to the region and tracts involved, the tendon reflexes of the legs usually being increased with the disease at a level above the lumbar enlargement. When paraplegia has set in, sphincter disturbance is the rule. The course is progressive and rapid, the average duration being six to seven months. Death in most cases is caused by pulmonary or acute miliary tuberculosis; in others by sepsis from bed sores and infection of the urinary tract.

Prognosis.—The prognosis is extremely bad. I can find in the literature only one case report of recovery.

Treatment.—The one case of recovery referred to is reported from Switzerland by Veraguth and Brun,[4] that of a man 32 years old, who had been treated for pulmonary tuberculosis four years prior to the onset of cord symptoms. The latter first consisted of stiffness and pain in the left side of the neck, followed by the development of a Brown-Séquard syndrome, with paralysis of the left extremities and anesthesia of the right ones. Two months later laminectomy in the neck was performed and a thickly encapsulated solitary tubercle measuring 17 by 11.5 by 9.5 mm. removed from the interior of the cord on the left side. When the dura had been incised only a diffuse swelling of the cord was noted, but after incision of the pia the nodule was readily shelled out "like the yolk from a hard boiled egg." The

4. Veraguth and Brun: Cor. Bl. f. schweiz. Aerzte, 1910, **40,** 1097.

recovery was very rapid. Krauss and McGuire[5] also report a case in which an intramedullary tubercle at the fifth thoracic segment was readily removed, but the patient died a few hours after the operation.

REPORT OF CASES

CASE 1.—*Conglomerate tubercle in midthoracic region: Onset with epigastric paresthesia, then girdle pains, numbness and weakness of legs, finally picture of transverse lesion. Much pus in urine, but no pulmonary symptoms. Tuberculosis not recognized during life. Death seven months after onset. Necropsy: Pulmonary and genito-urinary tuberculosis. Conglomerate intramedullary tubercle at level of seventh thoracic vertebra. Numerous tubercle bacilli in sections from cord.*

History.—A telephone lineman, aged 35, was admitted to the service of Dr. Frank Billings in the Presbyterian Hospital, Jan. 6, 1916. I am indebted to Dr. Billings for the privilege of seeing and reporting the case. The family history was negative.

Previous History.—Measles and whooping cough in childhood; maxillary sinus infection on both sides four years prior to admission. The patient never had a trauma and gave no history of cough, fever, chills, sweats, abdominal pain or loss of weight.

Present Illness.—About Dec. 1, 1915, he began to notice a peculiar sensation in the epigastrium, which would disappear on rubbing the abdomen or walking. At first this sensation was only noticed on awakening. A few days later he noticed a girdle sensation and pain at the level of the lower ribs on both sides. In another few days this was followed by numbness in the sole of the right foot and rigid extension of the toes. After three or four days the numbness had reached to the knee and the left foot became similarly involved. December 22 the legs were so weak that he fell to the ground when he stepped from a wagon. The weakness progressed rapidly. December 24 he could still walk a little with the aid of a cane, but by January 2 he could not move the legs at all. By this time the numbness had ascended to the level of the costal margin on both sides. He also developed involuntary urination and obstinate constipation. When cathartics were given, involuntary defecation would result. There were occasional involuntary contractions and rigidity of the legs and twitching movements in the right lumbar muscles. Pain was not a prominent symptom, but there were occasional rather sharp, shooting pains radiating from the groins upward to the abdomen.

December 28 the patient was examined by Dr. L. F. McBride, whose chief findings were as follows: Spastic paralysis of both lower extremities with exaggerated knee jerks and bilateral ankle clonus. There was a saddle anesthesia and hypesthesia from the costal margin down. Blood: Wassermann reaction negative; red cells, 5,000,000; white cells, 10,000; hemoglobin, 87 per cent. Cerebrospinal fluid: Wassermann reaction negative; 30 cells per cubic millimeter; Nonne globulin test strongly positive. Urine: Albumin present; 30 to 40 leukocytes per cubic centimeter; a few hyaline and granular casts were found.

Condition on Admittance Jan. 6, 1916.—Complete paralysis of both legs. Loss of tactile and pain sense below the level corresponding to the eleventh intercostal nerve area, except that very slight tactile sensation remained on the inner surface of the thighs, soles of the feet and perineum. Sensation to heat and cold was also lost and there was complete loss of muscle sense in the legs.

The pupils and eye muscles were normal. The tonsils appeared diseased and the left one contained pus. Culture from the tonsil yielded hemolytic streptococci.

Examination of the lungs and heart was negative. The liver and spleen were not palpable. The abdomen was lax. There was no abdominal tenderness and

5. Krauss and McGuire: Jour. Am. Med. Assn., 1909, **53,** 1911.

nothing abnormal could be felt. January 6, blood examination: Red cells, 4,200,000; white cells, 7,200; hemoglobin, 80 per cent.; blood pressure, systolic, 150; diastolic, 100; urine, acid, with trace of albumin; numerous leukocytes, but no casts were found; temperature and pulse rate, normal.

Examination was made by me Jan. 14, 1916, when the following notes were dictated:

No voluntary movement in lower extremities. With the arms folded on the chest the patient can raise his head and shoulders slightly, and in making the

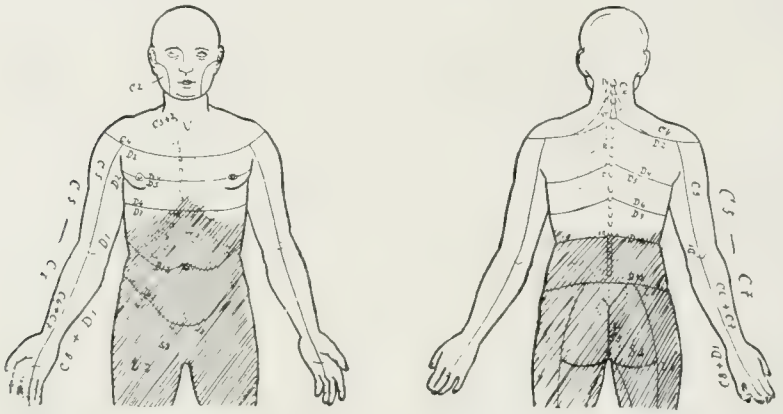

Fig. 1 (Case 1).—Sensory chart. The shaded portion indicates anesthesia to touch.

attempt the umbilicus moves 1 inch upward (Beevor's umbilicus sign). Abdominal reflexes not obtained, but on tapping the lower ribs, contractions in the oblique muscles are occasionally seen. The knee jerks are increased, with slight indication of clonus on the left side. Ankle jerks slightly increased. On stroking the soles of the feet slight extensor response of the big toe is obtained, together with a very marked "defense movement," consisting of flexion and adduction at the hip, flexion of the knee and extension at the ankle and slight flexion of the small toes. Direct myotatic irritability increased in the entire musculature of both lower extremities. Vesical sphincter much relaxed, as any movement

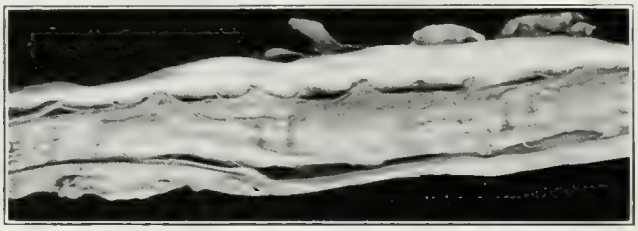

Fig. 2 (Case 1).—Fusiform enlargement of cord marking location of tubercle

is apt to cause dribbling of urine. Upward border of tactile anesthesia is at a level 1½ to 2 inches below the ensiform cartilage, that of analgesia 2 inches higher (Fig. 1). Pressure and muscle sense also lost in both legs. Diagnosis: Transverse lesion at about seventh or eighth thoracic segment; incomplete, as tendon reflexes are not abolished. Lesion probably intramedullary and of inflammatory nature, but pressure from without cannot be excluded even in the almost complete absence of pain.

Roentgen-ray examination of the spine was negative. Lumbar puncture, January 24, yielded a clear fluid with a cell count of three; negative Wassermann

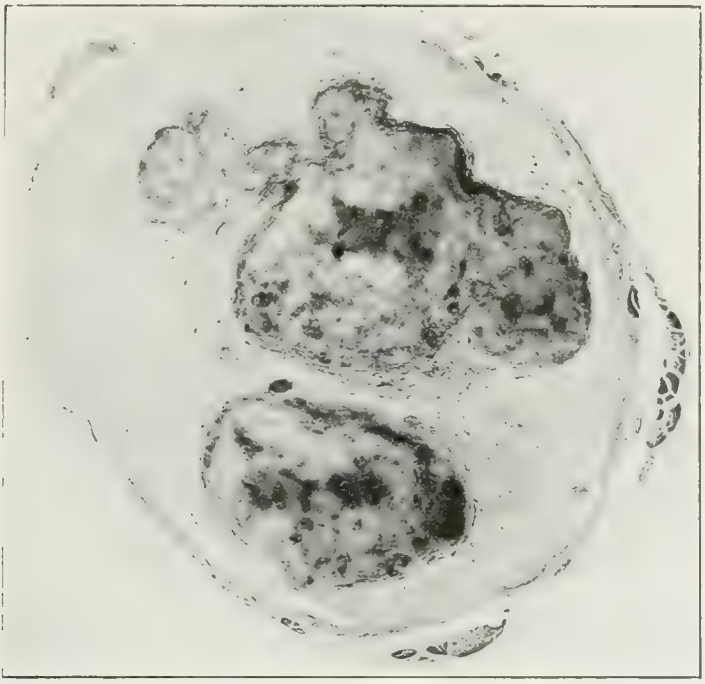

Fig. 3 (Case 1).—Cross section of conglomerate tubercle of cord showing two large caseous areas.

Fig. 4 (Case 1).—Tubercle bacilli in the cord. Carbolfuchsin

test; positive Nonne-Apelt globulin test. The Lange colloidal gold test was peculiar, no tube showing a change except the fifth (the dilution 1 to 160), which gave a definite reaction, the formula being 0 0 0 0 2 0 0 0 0 0.

February 17 the tonsils were removed; streptococci were obtained in culture. From this time on there was no material change in the nervous findings. The urine always contained much pus and the bladder was repeatedly irrigated with boric acid or protargol; later also with argyrol. There was an irregular fever, the temperature varying between subnormal and 102 F. The patient gradually grew weak and emaciated. No pulmonary symptoms attracted attention. The patient died July 25, 1916.

Necropsy.—The necropsy was held by Dr. B. O. Raulston, resident pathologist of the hospital, and the following anatomic diagnosis was recorded: Acute diffuse miliary tuberculosis of both lungs; chronic tuberculosis of the upper lobes of both lungs; extensive ulcerative tuberculosis of the left kidney; left perirenal abscess; nodular tuberculosis of the right kidney; tuberculosis of both ureters,

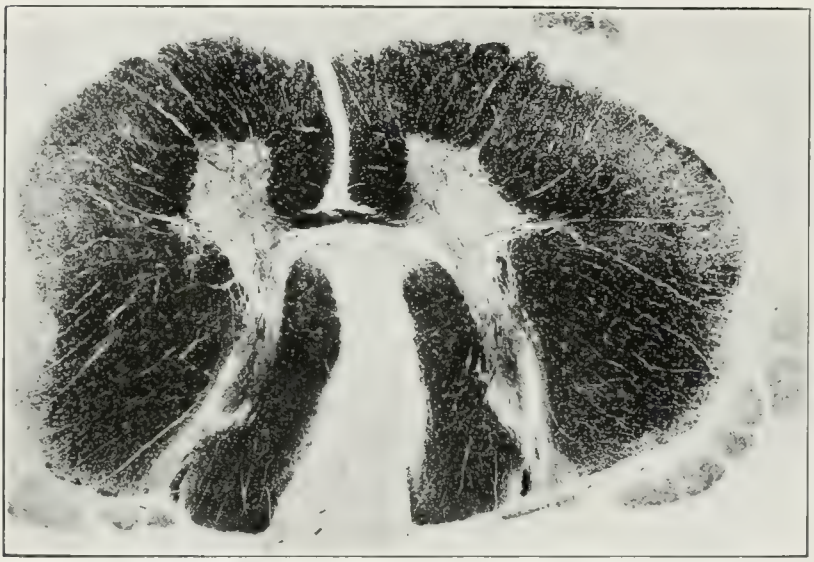

Fig. 5 (Case 1).—Ascending degeneration above level of tubercle. Pal-Weigert method.

urinary bladder, prostate and seminal vesicles; fistula between urinary bladder and rectum; tuberculosis of the spinal cord at the level of the seventh thoracic vertebra; marked shortening of the flexor muscles of both thighs; calcified tracheobronchial tuberculous lymph adenitis; marked anemia and emaciation; severe decubital necrosis; moderate hyperplasia of the spleen; cloudy swelling of the liver and myocardium; petechial hemorrhages on the gastric mucosa; hyperemia of the lining of the trachea and main bronchi.

The spinal column showed no change. The brain could not be examined.

Description of the Cord.—The dura shows no change except a fusiform bulging in the midthoracic region. It is also smooth internally and not adherent. The pia is slightly thickened and opaque in the thickened area, which measures 3 cm. in length (Fig. 2). The greatest width of the cord in this portion is 13 mm., while above and below it measures 10 mm. No nodules are seen on the anterior surface, but posteriorly at the lower end of the thickened area, pinhead sized grayish elevations are seen along the posterior roots on the left

side. On transverse section of the cord in the cervical region the columns of Goll are distinctly gray. In the lower thoracic and lumbar regions the lateral columns on both sides are distinctly gray.

In cross section of the thickened portion of the thoracic cord no trace of normal markings remain. About four fifths of the cross section is taken up by a firm, grayish-white tissue. Small wedge-shaped rests of cord tissue are seen near the median line anteriorly and on each side in the posterior horn region, posteriorly. Of the latter the left one is the larger. A section 1 cm. farther down shows only remnants of cord tissue in a half dozen places along the periphery—each not over 1 mm. in thickness.

Histologic Examination.—Cross section of the fusiform enlargement of the cord shows typical caseous tuberculosis (Fig. 3). All trace of the normal cord markings, even of the sulci, is lost. There are two large caseous masses sur-

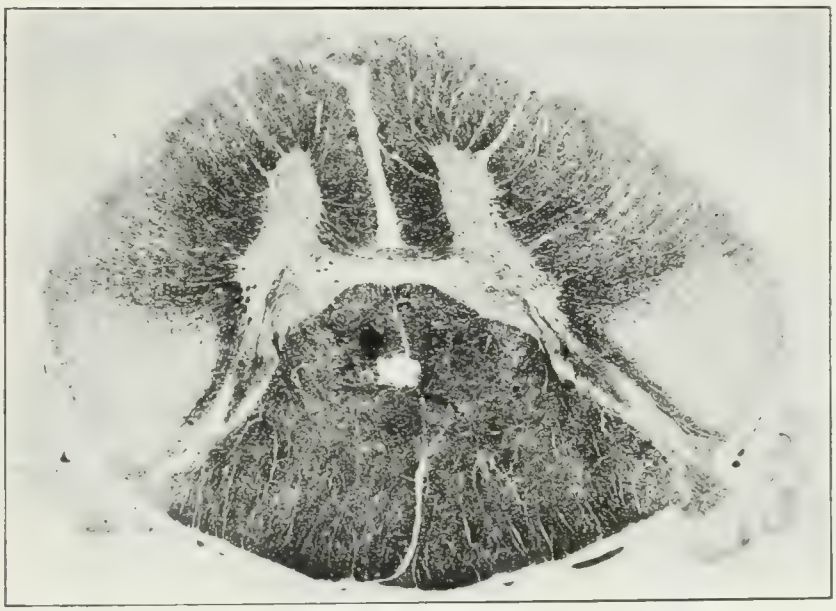

Fig. 6 (Case 1).—Descending degeneration below level of tubercle. Pal-Weigert method.

rounded by typical tuberculous tissue, rich in giant cells. Tubercle bacilli are extremely abundant in this tissue (Fig. 4).

Sections of the cord above and below the fusiform enlargement show only ascending and descending degeneration, most clearly seen in Pal-Weigert preparations (Figs. 5 and 6), but it is sufficiently recent to give excellent Marchi reaction as well.

II. COMBINED DEGENERATION OF THE CORD CAUSED BY VISCERAL TUBERCULOSIS

There exists in the literature reports of a fair number of cases of combined degeneration of the cord similar to that of pernicious anemia in which tuberculosis of various parts of the body outside of the

central nervous system seems to be the cause of the degeneration. The earlier literature is fully considered by Réné Sand,[6] who also reports a case of his own. Henneberg,[7] in his exhaustive article on "funicular myelitis" or "combined pseudosystemic degeneration" and "anemic focal leukomyelitis" comments on the relatively great rarity of such cord degeneration in connection with tuberculosis.

The following case appears to be one of this kind, though rendered more difficult and complicated by an old brain lesion apparently having no connection with the final illness.

CASE 2.—*Man of 46 years with history of stroke causing right hemiplegia five years before death. Only partial weakness left behind. Later, pain and weakness of right side, followed by paraplegia and sphincter disturbance. Increased tendon reflexes and Babinski sign. No pulmonary symptoms and only slight physical signs. Necropsy: Chronic pulmonary and pleural tuberculosis. Atrophy of brain and cord. Old hemorrhagic softening in left hemisphere. Nodule in left Sylvian fissure. Extensive bilateral cord degeneration.*

History.—A telegraph operator, 46 years old, was admitted to my service in the Presbyterian Hospital, April 29, 1915. The family history was negative as to tuberculosis.

Previous History.—Gonorrhea at 25; chancre denied; moderate user of alcohol. Eight years previously he had a severe cough for a month. Following this he had occasional frontal headaches and frequent dizziness for two years. After a week of much headache and dizziness he had a stroke in March, 1910. He was unconscious one day. The right arm and leg were paralyzed and he also had considerable pain in the right extremities. The speech was not affected, at least not to any marked degree. He walked again in three weeks, but some degree of weakness and occasional pain in the right side remained.

Last Illness.—For over a year prior to admittance there had been numbness and more pain and weakness in the right arm and leg. Following an operation for hernia and hemorrhoids in February, 1915, he grew weaker and entered the hospital in April on account of general weakness and the annoying sensations on the right side.

Examination on Admittance, April 29, 1915.—Weight, 150 pounds; pupils react to light and in accommodation; slight weakness of left internal rectus; grip in right hand slightly weaker than left; strength in legs about equal; moderate incoordination of hands and feet, more so on right side; wrist, elbow, knee and ankle reflexes brisk and equal; abdominal and cremasteric reflexes present, but weak on the left side; plantar reflex normal; no definite sensory disturbance; only slight lung findings, namely, relative dulness and mixed inspiration with bronchial expiration over left upper lobe; slight irregularity of heart action. Blood examination: hemoglobin, 87 per cent.; erythrocytes, 4,010,000; leukocytes 10,400. Urine negative except for a few pus cells. Wassermann test with blood and spinal fluid negative. The latter gave a cell count of 3 and negative Nonne-Apelt and Lange tests.

The patient remained in the hospital for three weeks and had normal temperature, pulse and respiration. He left the hospital, May 18 and returned Oct. 21, 1915, in a much worse condition. In June an abscess formed over one of the lower ribs anteriorly. This was incised and the patient had to stay in bed for a month. Afterward he was barely able to stand up and could not

6. Sand, Réné: Acad. roy. de méd. de Belg., Oct. 31, 1903.
7. Henneberg: Handbuch der Neurologie (Levandowsky), 1911, **2,** 769.

walk without help. The legs grew weaker but the pains were less troublesome than before. The fingers of the right hand became so numb and weak that he no longer could write. Slowness of micturition and occasional incontinence of urine and feces developed about three weeks before his return to the hospital.

Examination Oct. 21, 1915.—Marked general weakness and pallor; pupils react normally; weakness of left internal rectus; at 2 feet he could get binocular fixation with effort and retain it until a 5 inch point was reached, then the eye diverged. (Examination by Dr. E. V. L. Brown.) No gross limitation of visual fields; no nystagmus; no other cranial nerve weakness. Right arm slightly but distinctly, weaker than the left one, with considerable muscular rigidity,

Fig. 7 (Case 2).—Old brain lesions; hemorrhagic cyst in Sylvian fissure and hemorrhagic softening in insula.

especially above the elbow; considerable ataxia of both arms; more so of the right one. The patient could raise the head from the pillow but could not raise himself to a sitting position. The right thigh could be flexed on the abdomen with the heel dragging on the bed, but he could not lift the foot. Extension and adduction of the right hip were fair; abduction very weak. The knee could be extended when the thigh was supported; ankle movements fair; extension of toes weak. Left leg: Flexion of thigh as weak as on the right side, but abduction and adduction better. The heel could not be lifted from the bed unless the thigh was supported; ankle and toe movements fairly good.

Reflexes: Wrist reflexes present and equal; elbow reflexes increased, more so on the right side; abdominal reflexes not obtained; knee and ankle reflexes increased, more so on the right side; bilateral knee clonus present, but no ankle clonus; bilateral Babinski sign. Sensation: Tactile sensation lost below level of umbilicus; pain sense diminished below same level and temperature sense lost in both legs, but not on the abdomen; thorax rather hypersensitive.

The Wassermann test with the blood and spinal fluid and other tests on the latter were repeated and again reported negative. The luetin test also was negative. Hemoglobin, 66 per cent.; erythrocytes, 3,520,000; leukocytes, 6,300. Blood pressure: Systolic 100; diastolic 60. The urine contained numerous leukocytes and continued to do so. The sinus at the site of the old abscess reopened. Examination of the pus for tubercle bacilli was negative and the roentgen-ray examination revealed no bone lesion. The tuberculin test with 1 mg. of old tuberculin was negative; with 3 mg. the temperature rose to 100.2 F., and pain, tenderness and a little redness at the point injected were observed.

Fig. 8 (Case 2).—Thoracic cord. Degeneration in posterior and lateral columns. Pal-Weigert method.

The temperature occasionally rose to 100.5 F., and this rise was ascribed to the cystitis. The catheter had to be used every day. The patient gradually failed and died Dec. 19, 1915.

Necropsy.—The necropsy was held by Dr. Raulston. The chief findings were: moderate edema of the brain; general atrophy of the spinal cord; calcified plaque in spinal meninges; nodular caseocalcareous tuberculosis of the apex of the left lung; fistulous opening in the right lateral chest wall; right fibrous obliterative pleuritis; localized left fibrous pleuritis; calcified tubercles of tracheobronchial lymph glands; cloudy swelling of heart muscle; slight fatty changes in the lining of the aorta; passive hyperemia and cloudy swelling of kidneys; chronic purulent cystitis; passive hyperemia, fatty changes and cloudy swelling of the liver; tumor of right adrenal; passive hyperemia and hyperplasia of the spleen; petechial hemorrhages of the renal pelves.

The spinal cord and its dura weigh 30 gm. The dura shows little change; here and there slightly raised patches in inner surface and some roughening, but no thickening at point of contact with calcareous patch in arachnoid. This patch is situated along the posterior surface of the lower thoracic cord at approximately the sixth to eighth thoracic segment. It is 2.3 cm. long by 1 cm.

in greatest width and from 0.5 to 1.5 mm. in thickness. It is whitish, rough and of bony hardness. It is adherent to the dura. No other calcified areas are found and the pia arachnoid proximal to this area shows marked fibrous thickening and is grayish-white in color. The condition is most marked in the midthoracic region and gradually diminishes upward. The pia of the anterior surface has a normal appearance. The size and contour of the cord are normal only in the lumbar and sacral regions, where the gray horns are distinct. In the thoracic region below the calcified region the cord is flattened anteroposteriorly; 1 cm. below calcified patch the cord measures 1.2 cm. laterally and 5 mm. anteroposteriorly. The structure cannot be made out on cross section, which appears as an irregularly mottled gray and white surface. The same condition exists in the remainder of the thoracic region, although in the upper part the section shows a little more semblance of normal marking. The cervical region is markedly atrophic and even at the site of the cervical enlargement it is

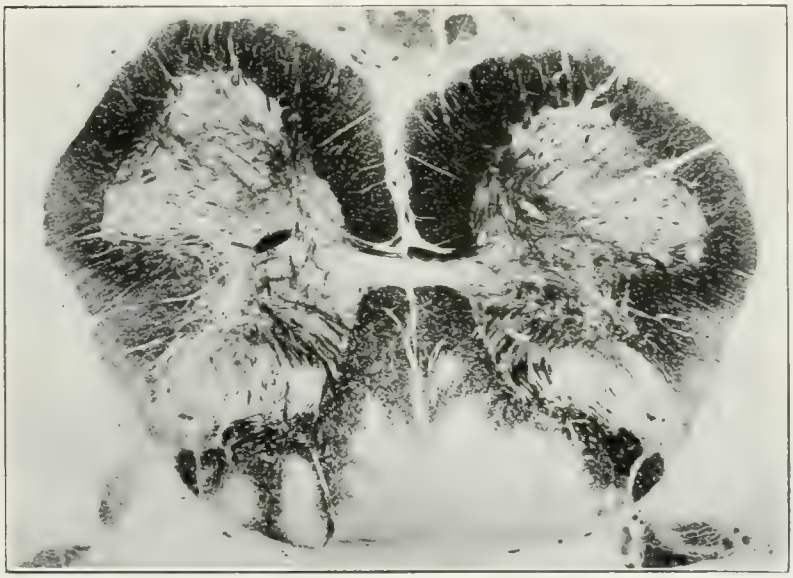

Fig. 9 (Case 2).—Lumbar cord. Degeneration mainly in posterior columns. Pal-Weigert method.

smaller than the lower thoracic and proportionately very much smaller than the lumbar portion. Brownish hemorrhagic and grayish-yellow degenerated areas are seen on the cut surfaces. The gray horns can scarcely be made out even in the upper cervical region. The bulb appears normal externally and on section.

The *brain* after formaldehyd hardening weighs 1,050 gm.

The dura shows no change. The pia over the convexity, especially in the vicinity of the paracentral lobules shows a fibrous thickening, more so on the left side. No other external change. On sectioning the brain shows an area of old softening in the right frontal lobe, which extends inward from the middle of the lateral border over half way to the lateral ventricle. It largely occupies the cortex, involves the insula and almost reaches the fissure of Sylvius. Just inferior to the area described the fissure of Sylvius contains a firmly adherent, smooth, oblong, grayish-white nodule which is about 1.5 cm. long

and 1 cm. in diameter. On section it has a firm whitish wall 1.5 mm. thick containing reddish-brown solid material (see Fig. 7). The cortex along the fissure of Sylvius shows superficial softening and brownish discoloration for some distance backward. In the left parietal lobe underneath the pia thickening described there is slight superficial softening. No other changes are found on the cut surfaces.

Histologic Examination.—Brain: The old focus of softening only shows pial fibrous thickening, destruction of cortex and replacement by a loose fibrous tissue with deposits of pigment. The nodule in the fissure of Sylvius has a hyaline, lamellated, fibrous wall, with small calcified areas. The contents are largely a hyaline mass with numerous slits (cholesterin ?) and granular masses suggestive of altered red blood cells. The vessels in the adjacent pia show fibrous thickening of the intima.

Spinal cord: The dura near the calcified plaque consists of only old fibrous tissue.

Weigert-Pal specimens show fairly symmetrical degeneration at all levels, involving chiefly the columns of Goll and Burdach and the tract of Gowers, but the crossed pyramidal tracts are also involved (Figs. 8 and 9). In the lumbar region the posterior roots show moderate degeneration. In the upper cervical region the small size of the cord is particularly striking; here the direct pyramidal tracts are much more degenerated than the crossed ones and the posterior roots show distinct degeneration. In the bulb the pyramids are normal but the degeneration of the posterior columns extends up to their nuclei. Hematoxylin-eosin and Van Gieson specimens only bring out the usual cribriform structure of the degenerated tracts and moderate thickening and hyaline change of the pial vessels.

30 North Michigan Avenue.

THE PITUITARY GLAND IN EPILEPTICS

THE CONFORMATION OF THE SELLA TURCICA *

Second Paper

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In an earlier paper Shaw and myself[1] described some pituitary glands from epileptics, our conclusions being that in epileptics the gland was below the average normal weight and that in it were islands of connective tissue, possibly connected with the blood-supply, but apparently not elsewhere described. We gave no description of the bony fossa in which the gland lies, other than to point out that the fossa was often decidedly larger than the contained gland.

Since the publication of our paper, Johnson[2] has described changes in the bony structures composing the sella turcica in epileptics, these changes consisting of a *roofing* of the fossa, *contraction* of the fossa itself, and a *thickening* or *increased density* of the bone bounding the sella. L. Pierce Clark[3] has noted this roofing in a few cases, but unaccompanied by corresponding changes in the physical make-up or variations in the type of the epilepsy.

On the especial basis of Johnson's work, there has grown up an impression that the pituitary gland in epileptics is compressed, or at least encroached on by the bony structures of the sella. This is held to support Cushing's[4] theories regarding hypopituitarism in epileptics.

At the Colony, several hundred necropsies left in my mind the distinct impression that no constant variation from the normal type was present, and in order to check up this impression a series of cases was carefully recorded.

Before presenting the material from this series, I would call attention to Figures 1 and 2, showing the anatomy of the sellar region.

Photographic records of the sella presented certain difficulties and

* Submitted for publication Jan. 25, 1918.

1. Munson, J. F., and Shaw, A. L.: THE ARCHIVES INT. MED., 1894, **14,** 393.
2. Johnson, G. C.: Am. Jour. Roentgenol., **1,** 172; *ibid.*, New York State Jour. Med., 1917, **16,** 559.
3. Clark, L. Pierce: Jour. Am. Med. Assn., 1914, **63,** 1655.
4. Cushing, H.: The Pituitary and Its Disorders, Lippincott & Co., 1912, p. 272.

finally the shape of the parts was recorded by tracing their outlines on glass, with pen and drawing ink. Two tracings were made, one by placing the glass flat on the base of the skull over the pituitary (corresponding to Figure 1), and the other by tracing the outline of the surface of the bone, after a sagittal saw cut in the median plane had permitted chipping away one side of the region. For this a sheet of mica was used because of its thinness and the outline afterward trans-

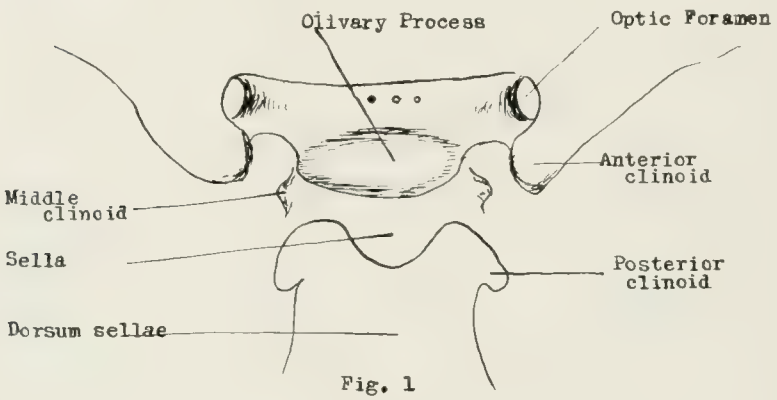

Fig. 1

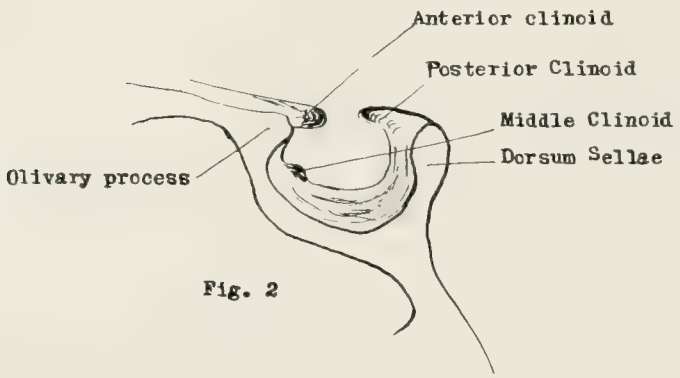

Fig. 2

Figs. 1 and 2.—Showing conformation of the sellar region. Reduced one third.

ferred to glass. These tracings may be preserved as such, or may be reproduced by contact through photographic processes. The material here presented has been collected entirely within the Craig Colony's necropsy service, mostly by myself, but in part by Drs. Shaw and Joy, to whom my thanks are due. The eighty-five cases presented are very largely consecutive and the omissions and additions from the series are due, with one exception, to reasons of expediency; in other words, this series does not represent selected material.

The line of vision of the roentgenologist and of the pathologist are different by 90 degrees. The roentgenologist views the sella along a line parallel to that joining the two external auditory meatuses — from the side; in this position the clinoid processes necessarily cast a shadow which seems to be above and across the hollow of the sella, and any increase in their length will give a shadow completely closing

Fig. 3.—The approximated finger tips used to represent the clinoids.

the mouth of the sella. The pathologist at necropsy sees these structures from above, along a line at right angles to that of the roentgenologist. The sella and its neghborhood are exposed flat to view and the actual relations of the parts can be seen; it will always be found that no matter how the clinoids overlap, they are laterally placed and always have between them an opening over the gland, covered by dura.

Fig. 4.—Representing the opening between the laterally placed clinoids.

In Figures 3 and 4 the approximated finger tips are used to represent the clinoids; in Figure 3 the finger tips are seen as the roentgenologist sees the clinoids, while in Figure 4, the large opening between the laterally placed clinoids is well shown.

Unfortunately, normal material has not been available to me for use as a standard. Through the courtesy of the late Dr. Gibson of the

University of Buffalo I was able to obtain some tracings of presumably nonepileptic sellas, shown in Figure 5. It is interesting to note the diversity of these sellas and to comment on the fact that in the normal material seen in the University's bone room, the middle clinoids were practically always distinctly present, while in our epileptic material the middle clinoids were practically always absent.

Only selected drawings (Figs. 8, 9 and 10) are reproduced with this article, but an inspection of the entire series shows that in the

Fig. 5.—Presumably normal sellas. Reduced one half.

epileptic there is no constant shape or type of sella, but that, on the contrary, there is a wide diversity. This will be shown by various tabulations:

TABLE 1.—General Conformation

	Cases
Average or large	61
Small	16
Average or normal depth	64
Shallow	13
Deformed	16

From the horizontal tracings we can predict what sort of shadow our cases would have cast on the roentgen ray plate. The *interclinoid gap* is the measure of this and is determined as follows:

The tips of the anterior clinoids are joined by a line. A line parallel to this is drawn through the most anterior portion of the posterior clinoids; the distance between these two lines is the interclinoid gap. Since the roentgen rays diverge somewhat, the shadow of the gap will be somewhat wider than the above measure, dependent

Weight mgs.	5mm	6mm	7mm	8mm	9mm	10mm	11mm	12mm	13mm	Total
200mgs		2		1						3
300			1	1	1					3
400		1	1	4	4	2	3	1		16
500				4	1	2	2	1		10
600				1	1	2	4	1	2	11
700					1	2				3
800							1			1
900										
1000mgs										

Fig. 6.—Relation of pituitary weight to anterior-posterior diameter of sella.

on the position of the tube. The results of this measurement are as follows:

TABLE 2.—Interclinoid Gap

	Cases
No gap	34
1 mm. or less	10
1 mm. up to 2 mm	16
2 mm. up to 4 mm	20
4.5 mm. up to 6.5 mm	5
Total	85

It must be admitted from this tabulation that roofing would appear in a majority of the cases of this series.

Before accepting this as evidence of compression, we must recall that the anatomist always sees an open space above the gland, filled

only by dura and bounded laterally by the clinoids. This space is clearly seen in the median sagittal sections, and measuring the narrowest portion of the aperture we have the following:

TABLE 3.—EFFECTIVE OPENING OF SELLA

	Cases
5 mm to 6.5 mm	11
7 mm. to 10.5 mm	54
11 mm. to 13 mm	12
Total	77

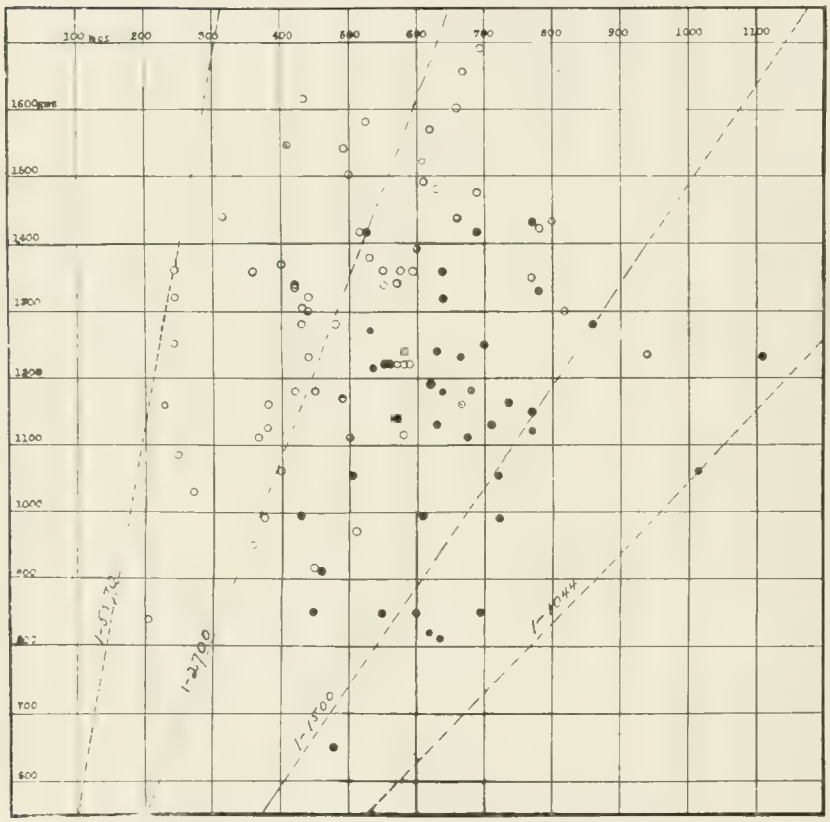

Fig. 7.—Showing beam weight and pituitary weight for males and females. Dotted lines show ratio to one part of pituitary. The circles are males; dots females.

The sella is bounded anteriorly by the olivary eminence and posteriorly by the dorsum sellae. These structures are sometimes so shaped as to narrow the opening of the sella, so that the effective opening is less than the greatest anterior-posterior diameter. The relations of these measurements are shown by a comparison of Tables 3 and 4, and the amount of overhang is shown in Table 5.

TABLE 4.—Anterior-Posterior Diameter (Greatest)

	Cases
5 mm. to 7.5 mm	9
8 mm. to 11.5 mm	62
12 mm. to 13 mm	6
Total	77

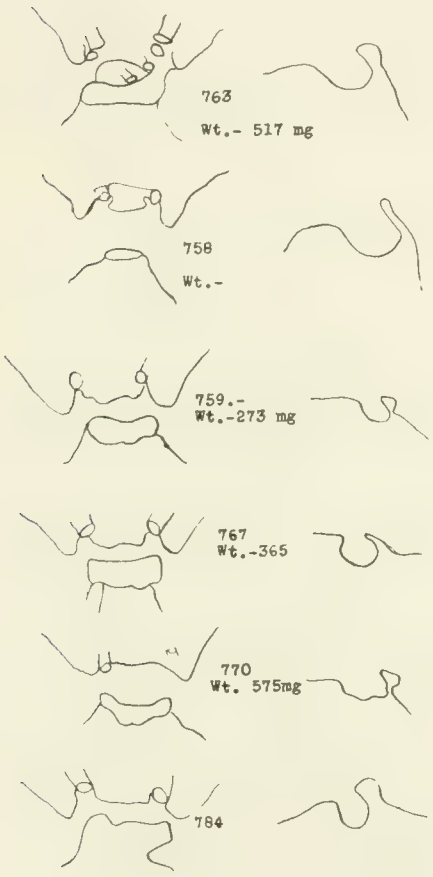

Fig. 8.—Diagrams showing the diversity in shapes of the sella in different epileptic subjects. Reduced one half.

TABLE 5.—Overhang (Antero-Posterior Diameter Greater Than Effective Opening)

	Cases
No overhang	41
Slight (about 1 mm.)	18
Some (about 2 mm.)	13
Marked (3 to 4 mm.)	5
Total	77

In addition to actual overhang, some limitation of the sella is produced by changes in the shape of the olivary eminence. This is shown in the anatomic drawing as a rounded prominence, but in many of our cases, its sagittal section shows a sharp angle at the anterior border of the pituitary, and even more important, the olivary eminence becomes possessed of lateral angular processes which tend to encroach on the cavity of the sella.

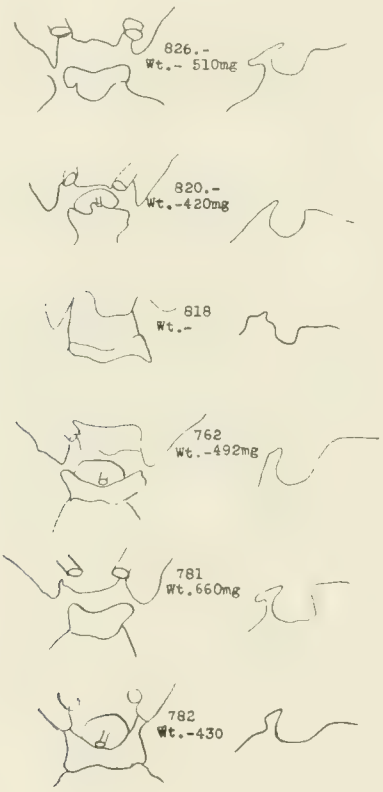

Fig. 9.—Additional types of sella in epileptics. Reduced one half.

The sellas have shown considerable variation in depth:

TABLE 6.—Depth

	Cases
5 mm. to 7.5 mm	17
8.5 mm. to 9.5 mm	42
10 mm. to 12 mm	9
Total	78

For comparison as to the size of the normal sella, the following figures may be quoted:

TABLE 7.—Normal Measurements

	Antero-Posterior	Transverse	Depth
Keith[5]	10 to 12 mm.	14 to 15 mm.	8 mm.
Dock[6]	6 to 10.5 mm.	.....	10 to 14.5 mm.
Biedl[6]	14 mm.	.....	5.5 mm.
Fearnsides[7]	10 to 12 mm.	.....	8 mm.
	Weight, from 590 mg. to 731 mg.		

Comparing these figures with those recorded from our series, it would seem that our cases run somewhat smaller than the normals.

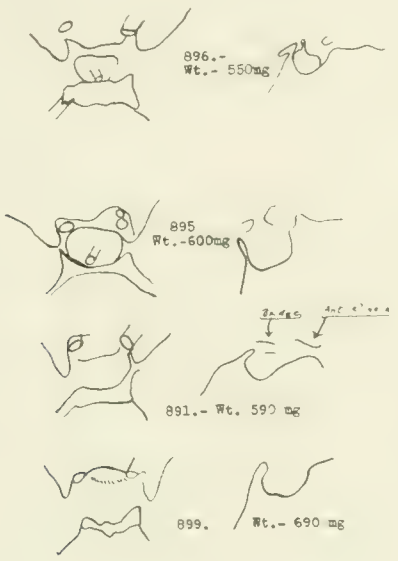

Fig. 10.—Types of sella in epileptics. Reduced about one half.

The weights of 116 glands have been recorded and are shown in the following tabulation:

TABLE 8.—Weights of 116 Glands

	Cases
Between 200 and 300 mm.....	8
300 and 400 mm.....	8
400 and 500 mm.....	26
500 and 600 mm.....	28
600 and 700 mm.....	28
700 and 800 mm.....	11
800 and 900 mm.....	4
1,000 to 1,100 mm.....	3
Total	116

It has been mentioned that the gland is often smaller than the sella in our cases.

5. Keith: Lancet, London, 1911, **1,** 993.
6. Quoted by Munson and Shaw, Footnote 1.
7. Fearnsides: Lancet, London, 1914, **2,** 16.

The relation of anterior-posterior diameter of the sella and the weight of the pituitary has been plotted in a few cases and shows (Fig. 6) that the weight of the gland and the diameter of the sella decrease together.

Another chart (Fig. 7) shows the relation of brain weight to the pituitary weight, by males and females. We see that female brains tend to run lighter in weight than the males, but that the female pituitary glands are distinctly heavier than those of the males. The ratios of these two weights are widely variable — from 1 part pituitary to 5,570 of brain tissue, to 1 to 1,044. The dashed lines shown in the figures are representative of the ratios indicated, and are drawn from the imaginary zero of the chart.

Certain deformities have been noted which may be briefly mentioned:

Middle clinoid processes were seen in only two of our cases.

The modifications of the olivary eminence by its overhang and by lateral angles have been mentioned.

Modifications in the shape of the dorsum sellae are numerous and are shown in the sagittal tracings especially. The shed-roof type, the grossly thickened, and the slender delicate represent wide variations of type. Notably, the middle of the dorsum sellae is lowered by a deep notch, sometimes extendinging almost to the floor of the sella.

The anterior and posterior clinoids not infrequently join each other in bony continuity; thus, five times on the right, once on the left and once both sides were thus joined. In addition, bony foramina for the internal jugulars are not uncommon and seem to be formed by bony bands between the anterior clinoids and the region where the middle clinoid should be. Spicules are also present in the dura continuous with the posterior clinoids.

In seven cases, there was very well marked asymmetry.

Once the anterior clinoid showed an exostosis.

Bony channels on the posterior surface of the dorsum sellae or extending transversely through it from side to side, and containing blood-channels, are not uncommon.

CONCLUSIONS

The sellas from a series of unselected epileptic subjects present a wide variation in type. The average size seems a trifle smaller than the figures given for normals and the contained gland seems to weigh less.

Roofing will be seen in the roentgenogram, but in reality the gland is well exposed and pressure seems a remote possibility. Bony changes are present but seem to be the anomalies which might well be present in a similar series of nonepileptic cases. There is no characteristic change to be seen in epileptic sellas.

THE INTRAVENOUS SERUM TREATMENT OF EPIDEMIC CEREBROSPINAL MENINGITIS

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The meningeal aspect of meningococcus infections has usurped such a prominent place in the commonly accepted ideas of the nature of epidemic cerebrospinal meningitis, that important facts have been kept in the background. The very name of the disease and the causative agent have given undue prominence to a single manifestation of a condition that in our opinion is very much more than a cerebrospinal meningitis. This is by no means a new idea. Others have from time to time expressed the opinion that meningococcus infections are primarily septic in nature and that meningitis is a secondary complication. So far as we are aware, however, this conception has not been adopted as a practical working basis for diagnosis or treatment. Such prominence has been given the meningitis that the premeningitic stage of meningococcus sepsis has been for practical purposes disregarded. It is our view that in a recognition of this primary stage of sepsis lies the key to early diagnosis and a more effective treatment.

This point of view has been forced on us by experience of an epidemic of 208 cases in the Base Hospital, Camp Jackson, and has been reached more or less independently by workers at the bedside and workers in the laboratory. The practical results have been the recognition of primary meningococcus sepsis in almost half of the cases before the characteristic selective action on the meninges has been exerted; the recognition of abortive cases or of other types of meningococcus sepsis not showing meningitis, the establishment of intravenous serum therapy on a firm basis with notable reduction of mortality and, further, the development of clinical and laboratory methods of diagnosis of proved value.

In making this report and in publishing conclusions that are at variance with some existing views we wish to make clear that much of this study was made under what were practically field conditions, in a hospital in the stage of organization, often without heat or even water, with inadequate ward and laboratory equipment and an overworked staff. Under these conditions in a certain number of the cases laboratory confirmation of the clinical diagnosis could not be had. We fully realize that an absence of finesse possible in civil conditions may

* Submitted for publication March 18, 1918.

well be a source of criticism of certain parts of our work and we wish publication made with that understanding.

Meningitis is a medical emergency. On prompt recognition and vigorous action the life or future wellbeing of the victim depends more than in almost any other acute disease. In order to insure early diagnosis, Lieut. Col. Kent Nelson, Division Surgeon, 81st Division, instructed the regimental surgeons to refer at once to the Base Hospital all men complaining of headache, fever, vomiting or other suggestive symptoms. Thus an incomparable opportunity for study of the early stages of these and other acute diseases was offered.

Symptoms and Signs.—Meningitis is preceded by a stage showing symptoms and signs of a generalized infection. This stage lasts from a few hours to three days—averaging about forty-eight hours. A few patients with this meningococcus sepsis never develop meningitis. These are usually either the abortive or the fulminating cases, rarely those with prolonged course. Recognition of the stage of sepsis depends on two kinds of evidence: (1) clinical, (2) bacteriologic. Approximately one half of our cases were recognized in the premeningitic stage. The clinical evidence of the incipient disease is, to the practiced observer, fairly definite, although for certainty laboratory confirmation is usually necessary. Description of the early symptoms or signs follows.

The fever is rarely above 102 F.—more often 99 to 101. The pulse is relatively slow, with frequent vagal irregularities. There is a characteristic attitude, manner and facies. The patient is not exactly irritable, but is resisting, prefers to be let alone and lies on his side with thighs and knees drawn up, shielding his face with the coverings. He is very sensitive to cold and resents exposure. The responses are intelligent, but are given in as few words as possible and with the least effort. The voice is not modulated; the muscles of expression are not brought into play. The voice and expression are "far away." There is a vacant look of apathy and dulness that is almost constant. The veins of the temporal region and forehead are full, the eyeballs are tender, and cyanosis of the face is most common. This is especially noticeable in the margins of the ears which are purplish in the region of the helix, antihelix and lingula, often with a sharp line of demarcation. The pupils are almost always dilated. A few cases show slight retinal edema with faint obscuration of the disk margins and fulness of the retinal veins.

In a large proportion of the cases there is an upper respiratory tract infection, a coryza, pharyngitis, tonsillitis, laryngitis; rarely bronchitis; in four cases a pneumonia. This respiratory involvement is so noticeable that it is more than a coincidence and demands careful

study. This was noted in our preliminary report,[1] also by Medlar,[2] Mink,[3] Thomsen and Wulff.[4] The oral secretions are often viscid in the extreme, the tongue coated, the breath heavy.

The skin manifestations are most important. Early there may be a more or less diffuse mottling, giving a lead-colored appearance. *Tâche cérébrale* is constant but of slight value in diagnosis. A few cases, mostly of the milder type, have shown a macular rash resembling early chickenpox or large rose spots. This rash is often very puzzling and characterizes the less severe types. The predominant skin sign is the petechial rash. This appears about the shoulder or pelvic girdle if at all; next in order of frequency, over the trunk, extremities, face, oral mucosa, and conjunctiva. We have not observed it in the retina. It appears with astonishing rapidity in crops, and in some of the severe cases the patient may become well dotted within an hour. The individual spots are typically petechial, the larger are raised above the skin surface, do not disappear on pressure, vary in size up to 1 cm. in diameter and last about three days, leaving a pigmented stain. In the presence of an epidemic, such a rapidly developing hemorrhagic rash is diagnostic. Purpura is a feature of the fulminating cases. This purpura does not arise from the petechial spots, but is a separate lesion. It develops with the greatest rapidity, and within a few hours considerable areas of the body surface may be covered.

Next to the rash, the reflexes give the most valuable early evidence of the disease. In a word, there is an unequal enhancement of the deep reflexes. The epigastrics, the knee jerks, the Achilles jerks, all tend to be exaggerated, with inequality. In a study of the deep reflexes of the early stages of acute disease in our receiving ward, such increased reflex irritability is found to be common in a variety of infections. This increase, however, is uniform on both sides of the body. The feature of the altered reflex irritability of meningococcus infection is the lack of uniformity of corresponding reflexes on both sides. One case began with a picture resembling that of an acute articular rheumatism; another with that of an acute, purulent meningococcus conjunctivitis. Slight chills are common. Headache is present in about 85 per cent. of the cases. It is frontal or vertical, less often lower occipital, may be most severe, and is described as a sense of unbearable pressure or "bursting." It is important to note

1. Herrick, W. W.: Epidemic of Meningitis at Camp Jackson, Jour. Am. Med. Assn., 1918, **70,** 227.

2. Medlar, E. M.: Epidemic Cerebrospinal Meningitis at Camp McClellan, Jour. Am. Med. Assn., 1918, **70,** 458.

3. Mink, C. J.: Points in the Epidemiology of Meningitis; abstr., Jour. Am. Med. Assn., 1916, **66,** 463.

4. Thomsen, O., and Wulff, F.: Meningococcus Infection and Meningitis, Hospitalstidende, 1917, **60,** 1192; abstr., Jour. Am. Med. Assn., 1918, **70,** 498.

that rigid neck, Kernig, and Brudzinski are almost always absent during this stage.

The clinical suspicion aroused by any combination of two or more of the signs or symptoms enumerated demands lumbar puncture. In the stage of sepsis, the spinal fluid is usually clear, shows in about 60 per cent. of the cases a slight increase in pressure, a normal number of cells, reduces Fehling's solution, and may or may not show a trace of globulin. Examination after long centrifugation and the evaporation on the slide of several cubic centimeters of the residue remaining after pouring off the supernatant fluid generally reveals one or more pairs of meningococci, almost always extracellular and variable in form and size. As noted in our preliminary report,[1] repetition of lumbar puncture within a short time often results in bringing down the organisms which, in our opinion, are first present in the cerebral-intraspinal spaces and find their way into the lower spinal spaces only after lapse of several hours. By special methods recently published[5] Capt. F. W. Baeslack, chief of the laboratory, has found meningococci by blood culture in this early stage in 36 per cent. of the cases so examined.

Clinical types of meningococcus sepsis. — Four types may be described — the abortive or atypical, the ordinary, the severe, the fulminating.

The abortive types: These are mild systemic disturbances without local focus of suppuration. Many of these patients have symptoms and signs of meningeal irritation. They may present themselves with headache and vomiting, may show a stiff neck, a positive Kernig and increased reflexes, slight fever and evidence of infection of the upper respiratory tract. They do not have the rash. The spinal fluid may be under increased pressure, but shows no abnormal elements and generally no meningococci. The diagnosis depends on the clinical picture and the demonstration of the meningococcus in the spinal fluid, nasopharynx, conjunctivae or blood stream. One of these patients who had evidence of meningismus showed an extraordinary high agglutinin titer of the blood. The brevity of the duration of these cases is surprising. Within twenty-four hours most of them are well; rarely they remain in bed forty-eight hours. Their importance is naturally epidemiologic. Doubtless in a large epidemic many such cases are undiscovered, being passed over as harmless, upper respiratory tract or other infections. They are, therefore, a great menace to susceptible contacts. They prove the importance of careful study of every case showing fever and any minor disturbances during the presence of an epidemic. The atypical cases are of peculiar interest and will be made the subject of a special report. One of these took

5. Baeslack, F. W.; Bunce, A. H.; Brunelle, G. C.; Fleming, J. S.; Klugh, G. F.; McLean, E. H.; Salomon, A. V.: Cultivation of the Meningococcus Intracellularis (Weichselbaum) from the Blood, Jour. Am. Med. Assn., 1918, **70,** 684.

the form of a subacute polyarthritis with positive blood culture, a somewhat prolonged course and a prompt response to large doses of serum intravenously. Recovery was complete.

The ordinary type: In these cases the symptoms of the generalized infection usually last thirty-six to seventy-two hours. They are as a rule, mild, the rash is usually slight and may be petechial or macular, never diffusely purpuric. The evidence of meningitis develops gradually; unconsciousness is rare, and the course may be prolonged. The chief emphasis is on the meninges. These cases show the typical headache, stiff neck, positive Kernig and Brudzinski signs; altered reflexes, irritability and the purulent spinal fluid. Hydrocephalus is a considerable danger and the response to intravenous serum therapy is often less prompt than in the more severe types.

The severe type: The stage of sepsis usually lasts from eight to forty-eight hours, during which there is evidence of severe toxemia. Patients are depressed, uncommunicative and wish to be left alone. The upper respiratory tract infection is frequent, with a viscid condition of the oral secretions. Fever is rarely above 102 F. The feature of these cases is the petechial rash, which appears with the startling rapidity described. The patient is profoundly prostrated, and, as a rule, becomes unconscious before any evidence of secondary suppurative foci in the meninges or elsewhere can develop. Polyarthritis is common in these serious types. Death may occur before any such metastases arise. Response to intravenous serum treatment is, as a rule, prompt. The most brilliant results with this method are in these grave cases. Few therapeutic experiences are so immediately satisfactory. The patients often rouse from coma, the rash and other symptoms rapidly recede and within forty-eight hours many are apparently out of danger. Intraspinous serum administration alone is usually insufficient to check their downward progress. Diagnosis in the premeningitic stage is usually possible. The blood culture is generally positive.

Fulminating cases: These are tragic in the extreme. The patient is overwhelmed with a toxemia and may die within a few hours. One of our patients lived only four hours after onset of symptoms. Another who suffered with a "cold" for three days went to bed at night with slight malaise and was found dead by his fellows early the next morning. These patients have a temperature of from 102 to 104 F.; a rapid pulse, vomiting, delirium, the petechial rash, and, most characteristic of all, extensive purpura. As a rule meningitis is not present. Clinical evidence, which may or may not be definite, is readily confirmed by blood culture or by demonstration of meningococci in the spinal fluid. In some cases the spinal fluid obtained by lumbar puncture shortly before death has been negative, while that obtained from the lateral ventricles immediately after death has shown meningococci.

This emphasizes the importance of our recommendation that lumbar puncture be repeated in doubtful cases to bring down the organisms for diagnostic purposes.

The complications.—The manifold complications of this epidemic have constituted a strong argument in favor of the view that the disease is primarily a sepsis. The purulent character of many of these cases is important. After the symptoms of the generalized disease subside such complications may continue to act as a nidus of infection from which relapses may arise or a general toxemia result, retarding or preventing recovery. Proper surgical or serum treatment of such a focus is of the greatest importance. Nine patients had panophthalmitis. The infection reaches the eyes through the ciliary vessels, not the optic nerve sheaths. The cornea becomes congested, the iris cloudy. Soon the media become opaque, and within a few hours sight is lost. The rapidity with which the entire organ is invaded and destroyed is a strong argument for the view that the infection is hematogenous. Fortunately, but one of our patients suffered a bilateral panophthalmitis. Enucleation has been performed in most of our cases with great improvement in the general condition of the patient. The affected eye is a source of pain, of mental and nervous irritability and other evidence of toxemia. On microscopic examination these eyes show meningococci in astonishingly large numbers. Optic neuritis and retinitis are present in some degree in a large number of cases and are of value in early diagnosis. Paralysis of the extrinsic muscles of the eye, most often those supplied by the sixth nerve, has been noted in six cases. One of these was bilateral, five were transitory.

We have observed but one case of endocarditis. This patient developed a relapse with dilated heart, a loud systolic murmur over the precordium, symptoms of sepsis and a positive blood culture. At necropsy a few small fresh vegetations were found on the tricuspid valve. The myocardium seems to suffer little. The pulse rate is slow during the early stages, often rapid during convalescence. There were six cases of dry fibrinous pericarditis. One of these at necropsy showed the most extensive possible deposit of fibrin in masses, some 5 cm. in diameter, over the visceral and parietal layers. Two cases exhibited pericardial effusion as a late complication. One patient had a temperature ranging to 104 F. One hundred and ten c.c. of bloody purulent fluid were removed, showing meningococci in pure culture; 30 c.c. of meningococcus antiserum were injected into the pericardial sac with prompt relief of symptoms and disappearance of meningococci in the fluid subsequently aspirated. Separate report will be made of these pericardial complications.

Pulmonary lesions are not at all uncommon. Three patients showed at onset consolidation of part or all of a lower lobe; one a small pleural effusion from which meningococci were grown.

Arthritis has been quite a feature of the epidemic. One case began as an apparent acute articular rheumatism; in two the arthritis preceded the meningitis, in others this complication appeared late. Arthritis in the stage of sepsis, is usually very painful, involves many joints, is not accompanied by much swelling or effusion, but shows local redness, heat and tenderness. The picture is almost exactly that of acute rheumatic polyarthritis, but is more transitory. The arthritis of the last stage is more generally monarticular, most often involving the knee, is purulent, accompanied by great swelling, but shows little redness and is only moderately painful. It is striking that despite the presence of a large purulent exudate in knee joints in the late stage of meningococcus sepsis, there is little muscular spasm or limitation of motion on account of pain. Repeatedly the meningococcus has been grown from the pus obtained in these joints. Serum has frequently been injected directly into the knee joints with apparent benefit. The prognosis of meningococcus arthritis, although a feature of the severe cases, is good and permanent disability is rare.

Otitis media has been common; none has required mastoid operation. At necropsy, the accessory sinuses of the nose are frequently found filled with pus which in a few instances contained meningococci. There have been three cases of monoplegia. Nine cases have shown epididymitis or orchitis. This has not been suppurative and has subsided in a few days without apparent atrophy. The postmeningitis cachexia is notable, although infrequent after intravenous therapy. There is emaciation, a waxy pallor of the skin, anemia, irritability, apathy, weakness and vertigo, tachycardia, exaggerated reflexes. In this condition it is of the highest importance to make a thorough physical examination. Often one of the complications enumerated above is discovered. Again, nothing can be found. Usually such patients recover after a prolonged period.

Two cases have relapsed; one four weeks after convalescence, another, three weeks. The second attack may be more severe than the first. A special report of these relapsing cases will be made. The fact of their occurrence lends discouragement to vaccine prophylaxis and other measures for the production of immunity.

A matter of highest importance is the recognition that epidemic cerebrospinal meningitis often occurs during the course of other acute diseases. The meningococcus seems to flourish in a soil prepared by any organism or by any condition that will lower the general bodily tone. A large number of our cases have developed during the acute stages or shortly after measles, pneumonia, otitis media, tonsillitis, or other infections of the respiratory tract. This association deserves special emphasis. Meningococcus infections as a complication of other acute diseases gives a confused clinical picture in many instances.

The diagnosis here naturally depends almost entirely on the laboratory. The clinical acumen must furnish the initial suspicion. The change of condition, the fatigue of travel, of unaccustomed drill, homesickness and other new influences to which the recruit is subjected doubtless act in a manner similar to acute diseases in paving the way for meningococcus infections.

Necropsy findings.—Among the fifty-four deaths in this series of 208 cases, thirty-one necropsies were performed. Owing to an overwhelming amount of clinical work and limited equipment, it was impossible to examine all of the dead. There was a remarkable dryness of the bodies. Section of the muscles resulted in little or none of the oozing usually seen. The peritoneum was often lustreless because of this lack of moisture. The lungs in many cases were dry and shrunken. The liver, spleen and kidneys, while enlarged in many instances, lacked the ordinary amount of fluid. This dehydration explains the excessive thirst of so many patients and is the basis of our routine ward order that water be offered every fifteen minutes to those awake.

Captain Blakeslee in several cases demonstrated that the exudate was subarachnoid and not immediately subdural. He has been unable to find necropsy evidence of suppuration about the cribriform plate of the ethmoid. In none of our cases did the macroscopic appearance suggest extension of the process from this point.

The following is a summary of the findings: Lack of lustre of the meninges without exudate, 1; purulent exudate in the central nervous system, 26; exudate localized in the vertex alone, 7; in the base alone, 3; vertex and base, 16; in the lateral ventricles, 10; parietal region alone, 5; occipital region or cerebellum alone, 0; congestion of meninges without exudate, 5; adhesion of meninges to cortex, 6; blocking of foramen magnum or ventricles, 6. The choroid plexus was in most cases congested and in more than half the number cystic. Eleven showed petechiae in the skin; 10, purpura. Diffuse purpura was not seen in the serous membranes, viscera or muscles. One case having athetoid and convulsive movements of the left side before death showed a large hemorrhage in the right Rolandic area with multiple small hemorrhages throughout the subcortical areas of cerebrum and cerebellum. Petechiae are frequent on both visceral and parietal surfaces of the pericardium and peritoneum. Four had conjunctival petechiae. Heart hypertrophy, 1; dilatation, 1; acute vegetative endocarditis (tricuspid), 1; pericarditis, fibrino-purulent, 4; sero-purulent, 4. Pleurisy was present in 8; lobar pneumonia in 2; bronchopneumonia in 8; lung congestion in 7; abscess in 1. The spleen was enlarged in 22 cases, normal in size 4; in 5 it was not examined. Kidney: cloudy swelling, 10; congestion, 10. Adrenal congestion, 1.

Liver, enlarged and congested, 17; showing cloudy swelling and fatty change in 5. Peritonitis, 1. Suppurative choroiditis, 3.

Treatment.—Based on the conception that the disease is in its early stages a generalized meningococcus sepsis which can be recognized before meningitis or other complications develop, the serum treatment, as established by Jochmann, Flexner and others has undergone modification at our hands. Instead of attacking a metastatic focus of infection in the meninges, we have sought to reach the organism during the stage of systemic invasion by intravenous serum therapy. This measure was at first tried as one of desperation in an attempt to save the life of a member of the staff of the Base Hospital who was stricken with a serious type of the disease. Success led us gradually to develop the present method. Having no standard criteria of such treatment, we have felt our way gradually until, with an experience of over 100 patients treated intravenously, we believe that a safe and satisfactory method has been worked out. Not only does clinical observation seem to justify the method to be described, but statistical study of cases treated by various methods shows that with the newer forms of treatment there is a decrease in mortality. Treatment in this epidemic has passed through three phases; the first phase, of intraspinal therapy alone; the second, of intraspinal combined with timid intravenous therapy; the third, of bold intravenous treatment combined with liberal drainage of the spinal fluid and the use of a considerable, though as a rule, a small amount of serum intrathecally.

On admission a patient presenting a combination of the early symptoms mentioned is subjected to lumbar puncture. If the spinal fluid is cloudy, enough is removed to reduce the intraspinal pressure to an approximate normal and a less amount of serum is at once allowed to run into the spinal canal. If the spinal fluid is clear, no intraspinal injection is made. The fluid is rushed to the laboratory in a thermos container and immediately examined. Meanwhile the patient receives a desensitizing dose to determine sensitiveness. One hour later 50 to 120 c.c. are administered by vein, the first 15 c.c. at the rate of 1 c.c. per minute. Large glass syringes are best for this, as the flow is easily controlled and a cumbersome arrangement of tubes and stopcocks is not necessary. In a case of ordinary severity this intravenous dose is repeated every twelve hours until the temperature becomes normal, or until six or eight injections have been given. In severe cases the serum is repeated every eight hours until the desired results are obtained. In fact, the size and frequency of intravenous serum doses is very like those advised by the group of workers in the Rockefeller Institute in lobar pneumonia of the appropriate type.

We have seen no ill effects from these large amounts of meningococcus antiserum. In a retrospect of the epidemic, our regrets are that

so many cases received doses too small. If given at all by vein, the serum must be boldly used. Study of Class B cases would seem to show that small amounts may have even a harmful effect. It is our belief, however, that this is not the case. In a few cases the temperature is seemingly not influenced by the intravenous injections. In such the type of serum is changed, an interval of about forty-eight hours is allowed to elapse and another series of doses given. So soon as meningitis develops the usual intraspinal injections are given and repeated about once in twenty-four hours for a varying number of days until the organisms disappear from the spinal fluid and lymphocytes make their appearance in numbers. With large intravenous injections of serum the meningococci, as a rule, disappear from the fluid within twenty-four to forty-eight hours and repeated intraspinal serum administration is not deemed necessary. The greater our experience in intravenous serum therapy in this disease, the more have we attempted sterilization of the blood by massive doses of serum, particularly in the early stages when the positive blood culture and the clinical picture indicate a generalized hematogenous infection. When meningitis is established, this treatment is supplemented by repeated spinal drainage, puncture usually being done about half an hour after the intravenous injection. Serum is introduced into the spine in amount sufficient to relieve the severe headache which may follow such drainage. It is our idea that by thus draining the spinal canal considerable antibody may escape from the blood stream into the upper intraspinal spaces through the choroid plexus. Experimental and clinical study of this point is in progress.

It is possible to overdo treatment. Some of the more prolonged cases, even when meningococci persist in the spinal fluid, do better or even recover promptly when all treatment is stopped. This is especially true of the cases that have little fever and in which the serum seems to act as an irritant giving rise to headache, delirium and increased opisthotonus. Other treatment is not neglected. Second in importance to serum is morphin, which should be freely used, especially in the early stages. Chloral and bromid are of minor help in controlling symptoms. Nervous patients are given opiates, with or without chloroform, before puncture is made. No patient is forcibly restrained during puncture. Large amounts of fluid and liberal nourishment are provided.

Table 1 shows that the total mortality of the entire series of 208 cases is 26 per cent. In the 129 cases treated by intraspinal methods alone or with intravenous serum doses of 10 to 45 c.c., it is 31.7 per cent.; in 79 treated by larger amounts of serum intravenously and average or smaller amounts intrathecally, 16.4 per cent. The mild cases do well by either method of treatment. It is in the severe types that the intravenous methods give the most striking results. Sixty-two

TABLE 1.—Epidemic Cerebrospinal Meningitis

March 4, 1918. 208 Cases

Class	Cases	Deaths	Mortality, per Cent.
A1a	36	1	2.7
A1b	17	0	0.0
A2a	15	12	80.0
A2b	24	12	50.0
A	92	25	27.0
B1a	7	0	0.0
B1b	5	0	0.0
B2a	5	2	40.0
B2b	20	14	70.0
B	37	16	43.2
A and B	129	41	31.7
C1a	11	1	9.9
C1b	4	0	0.0
C2a	17	2	11.3
C2b	47	10	21.1
C	79	13	16.4
A, B and C	208	54	26.0

KEY TO TABLE

Class A: Cases having intraspinal serotherapy alone.

Class B: Cases having the usual intraspinal serotherapy and small amounts (10 c.c. to 45 c.c.) of serum intravenously.

Class C: Cases treated with large amounts of serum intravenously with average or small amounts intraspinally.

1. Mild cases.

2. Severe cases.

a. Cases with early diagnosis (recognized before the spinal fluid became cloudy).

b. Cases with later diagnosis (recognized after the spinal fluid became cloudy).

and five-tenths per cent. of the serious cases in Classes A and B died; 18.5 per cent. of corresponding types in Class C. Another important effect of intravenous therapy is the apparent reduction in number of complications; 31 per cent. of Class A and B cases showed important complications; 14 per cent. of Class C.

It may be argued that Class C cases were those from the later stages of the epidemic when the meningococcus might have lost some of its virulence and that the results of intravenous serotherapy are therefore, not better than might have been reached with older methods. The possibility is admitted, but is not considered by us a probability. Clinically the cases studied in the later phases of the epidemic seemed about as severe as those seen earlier. One of the last of our deaths was a fulminating case with purpura.

Table 2 shows certain facts of interest. It is, however, misleading in that the Class C cases would appear to have received the most active

intraspinal treatment. It is to be borne in mind that report is made of the development of a method rather than of the method itself. This development extended throughout four months of a large epidemic and a sharp line of separation between various phases of this development is not possible. The tables do not, therefore, nor do the descriptions, represent the final method adopted or its results. In a future publication it is planned to take this up in detail. Table 2 is proof that intraspinal treatment has not been neglected, but it does not correctly indicate the amount of serum given by vein or spine in the fully developed combined method. In order to avoid too detailed classification we have arbitrarily placed every case receiving more than 50 c.c. of serum by vein in Class C. Most of our patients are now given from 200 to 600 c.c. by vein and a lesser average amount intraspinally than the table indicates. It is important to note the shorter period of fever and the earlier average disappearance of meningococci from the spinal fluid in Class C. It is a common experience to have organisms disappear from the spinal fluid after the first or second massive intravenous serum injection. The laboratory workers made special remark of this fact when such treatment began to be used freely.

TABLE 2.—Summary of Classes A, B and C

Class	Average Number Spinal Punctures	Average Amount Spinal Fluid Out, C.c.	Average Amount Serum in Spine, C.c.	Average Amount Serum in Veins, C.c.	Average Duration of Fever, Days	Average Duration of Meningococci in Spinal Fluid, Days
A and B	4.6	180.2	110.5	38	9	5.5
C	7.2	279.5	138.4	151	7.3	3.1

Ventricular puncture was not done. The rapidity with which formation of spinal fluid occurs makes a single puncture of one ventricle rather futile. The anatomic situation found at necropsy bears out this impression. The effect can be but brief and the operation is one of some magnitude. First Lieut. S. A. Cobb, M. R. C., has devised a method of starting the flow in cases in which it is impossible to secure more than a few drops of thick fluid in patients beginning to show signs of blocking of foramina. Chloroform is given, relaxing spasm of the neck muscles. Lumbar puncture is then done and the head manipulated with the idea of breaking up adhesions that may be forming about the foramen magnum and floor of the fourth ventricle. Necropsy study has shown that it is possible to achieve appreciable mobility of the region. The method is often successful in starting the flow and in one instance brought about resumption of respiration when this function had ceased. In this case life was apparently saved. Liberal drainage in the cases with prolonged course, and the use of Lieu-

KEY TO TABULATION OF MENINGITIS CASES IN TABLE 3

Class A: Cases having intraspinal serotherapy alone.

Class B: Cases having the usual intraspinal serotherapy and small amounts, 10 c.c. to 45 c.c. of serum intravenously.

Class C: Cases treated with large amounts of serum intravenously with average or small amounts intraspinally.

1. Mild cases.

2. Severe cases.

a. Cases with early diagnosis (recognized before the spinal fluid became cloudy).

b. Cases with late diagnosis (recognized after the spinal fluid became cloudy).

TABLE 3.—Data of 208 Cases—

Class	No.	Name	Duration of Fever, Days	Developing During or After: A. Pneumonia	B. Mumps	C. Measles	D. Others	Symptoms During Onset and Course of Disease: 1. Headache	2. Nausea	3. Vomiting	4. Chills	5. Delirium	6. Convulsions	7. Fever, F.	8. Pulse	9. Arthritis	10. Coryza	11. Sorethroat	12. Pneumonia	13. Cough	14. Unconsciousness	15. Eruption	16. Backache	No. Showing Important Comp.: A. Panophthalmitis	B. Arthritis, Mono.	B. Arthritis, Poly.	C. Paralysis, elsewhere
A1a	1	Clary	18				Otitis R	+		+				105.3	136		+	+									
	2	Grubb	6					+						99.2	80												
	3	Hickey	9					+		+				100.2	100								+				
	4	Hunter	6					+	+	+				101.0	116							+					
	5	Hooks	13					+	+	+	+			99.6	84	+											
	6	Hendrix	9				Otitis R	+						100.0	78		Nystagmus										
	7	Hawkins	8					−			+			102.0	126							+	+				
	8	Wall	0					F+						98.2	100								±				
	9	Wood	3					F+						102.4	122												
	10	Couch	1		+			F−		+				104.0	116								+				
	11	Harris	72*	+	+	+					+			98.0	78											+	
	12	Watkins	9					+		+				98.0	74								−				
	13	Allen	0					+		+				99.2	90												
	14	Epes	2					0+						100.2	80								+				
	15	Green	7	+		+								101.0	100		+	−					+				Deltoid
	16	Smith	2					+						96.0	100												
	17	Cone	2					F+			+			101.0	102			+								+	
	18	Crook	8								+			102.8	83											+	
	19	Marler	4					+		+	+			100.3	102												
	20	McNamara	9				Tonsillitis							97.4	98			+									
	21	Davis	6					F+		+				102.0	106						+						
	22	Moser	0		+									97.0	72							+					
	23	Bethea	4					F+						100.2	98			+				+					
	24	Ponds	6		+			+						99.0	86							+					
	25	Blue	4					F+						105.0	96								±				
	26	Reynolds	2							+				98.0	94			−									
	27	Self	14		+			0+						97.0	72						+						
	28	Moody	23								+			100.0	92								±				
	29	Delameter	5					+	+	+	+			101.8	72												
	30	Armfield	2					F+			+			102.8	76												
	31	Marlam	9					+						103.0	108												
	32	Williams	3					F+			+			101.2	100				+								
	33	Turner	12				Tonsillitis	+						104.0	110			±									
	34	Guley	9			+		F−						98.4	64												
	35	Larke	0					+						98.8	72												
	36	Lohse	2											103.1	102												
		Total	..	2	2	6	4	28	3	11	10	0	0	.....	...	1	2	7	1	0	2	6	9	0	0	3	1
		Average	6											101.0	90												
A1b	1	Bowden	2			+	+	F+	+					101.4	96								+	+			
	2	Tilley	21*					0+	+	+				99.6	84								±				
	3	Taylor	13			+		0+	+		+			108.0	92								±				
	4	Thorn	4		+			F+						100.0	90								+				
	5	Graham	5					F+		+	+			101.2	72												
	6	Rose	1		+			+	+					102.0	92								+				
	7	Bass	5					+		+				100.4	90												
	8	Warrenfells	3					+		+	+			100.4	90												
	9	Feezell	4					+		+	+	+		97.0	90								+				
	10	Harrelson	3					+		+				103.0	100								±				
	11	Mitchell	9					+			+			100.4	72								+	+			
	12	Burton	27			+		+		+				100.2	90												
	13	Crowell	4			+		+		+				100.4	88												
	14	Lail	0					+						98.0	76						+		+				
	15	Garland	2		+			F+						100.2	92												
	16	Slayton	3					+						98.0	78								+				
	17	Boyd	1			+		−						97.4	74			+					+				
		Total	..	0	3	5	1	17	4	8	5	1	1	.....	...	0	0	1	0	0	1	9	3	0	0	0	0
		Average	6											100.4	90												

Reflexes: N means normal; + means exaggerated; ++ means hyperactive; +++ means very hyperactive; R>L means right greater than left; 0 means absent.

* Other cause for fever.

—OF CEREBROSPINAL MENINGITIS

Number Showing Important Complications								Serum Effects								Reflexes (On Admittance)											Misc.	
C. Paralysis, Ocular	D. Epididymitis	E. Pneumonia	F. Pleurisy	G. Pericarditis, Dry	G. Pericarditis, Fluid	H. Otitis Media	I. Others	Anaphylaxis: Chill	Anaphylaxis: Collapse	Anaphylaxis: Dyspnea	Rashes: Erythema	Rashes: Urticaria	Rashes: Other Rashes	Adenitis: Cervical	Adenitis: Inguinal	Adenitis: Epitrochlear	Adenitis: Femoral	Neck Rigidity	Kernig	Brudzinski	Patellars	Achilles	Abdominal	Cremasteric	Biceps	Triceps	Babinski	Clonus	Photophobia	Herpes
						-R												+	R>L	0	+	+	+	+	+	+	0	0	0	0
												+		+				+++		0	N	N	N	N	N	N	0	0	+	0
												+						+	+	+	++	++	+	+						+
																		+	+		+	+					0	0		
	+					R-L		+										++	++	+	R>L	R>L	+	+	+	-	-L			
																		+	+		++						0	0		
Chicken pox							+			+		+						+	+											
	+																	0	0	0	+	+	0	0	+	+	+	0		+
												+																		
												+						+	+	0	+	+					0	0		
																		+	+	+	+	+	R>L	+	+	+	0	0		
																		+	+		+	+								
																		+	+	+	+	+	0	0	+	+	0	0		
																		+	+	+	+	+	N	N	+	+	0	0		
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						Unequal pupils												+	+	+	++	++	N	N	N	N	0	0		+
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TABLE 3.—Data of 208 Cases of—

Class	No.	Name	Duration of Fever, Days	Developing During or After: A. Pneumonia	B. Mumps	C. Measles	D. Others	Symptoms During Onset and Course of Disease: 1. Headache	2. Nausea	3. Vomiting	4. Chills	5. Delirium	6. Convulsions	7. Fever, F.	8. Pulse	9. Arthritis	10. Coryza	11. Sorethroat	12. Pneumonia	13. Cough	14. Unconsciousness	15. Eruption	16. Backache	No. Showing Important Comp.: A. Panophthalmitis	B. Arthritis, Mono.	B. Arthritis, Poly.	C. Paralysis, elsewhere
A2a	1	Williams	9											100.3	68		Lat. nystag.					+				
	2	Lynn	14		+			+						98.0	96					+	+					
	3	Clinton	D											97.4	74											
	4	Skelton	2D					+						102.0	94		+				+	+				
	5	Ellis	D					+						107.0	156						+	+	+			
	6	Murphy	D			−		+						101.0	120					+		+				
	7	Sells	D			−		+						103.0	70			−					+			
	8	Evans	D			−		F+					−	100.3	80								+	+		
	9	Packs	D					F+				+		103.2	100					+	+	+				
	10	Westfield	3					−	−	−	+			102.0	92						+	+				
	11	Frost	D			−		+						99.2	84		+			+			+			
	12	Hill	D			+								100.0	84					+						
	13	Buchanan	D								+	+		104.2	104			+			+	+				
	14	Meyers	D					F+		+	−			102.4	104											
	15	Bean	D									−		103.4	100		Purpura				−	+	−			
		Total		0	1	5	0	10	0	2	2	5	0			0	2	2	0	4	8	7	7	1	0	0	0
		Average	9											102.5	95												
A2b	1	Rich	19									−		98.0	100						+	−				
	2	Melden	D									−		100.2	92						+	−				Facial
	3	Cochran	13					+					+	96.8	98										+	−
	4	Sullivan	40*				Tonsillitis	+	+	+	+			99.0	86						+		−			
	5	McMillan	19					F+		+				99.2	112						+	+				
	6	Cook	42*					F+	+	+	−			101.0	100						−	+				−
	7	Smith	1					+			+	+		98.0	64		+									
	8	Thomas	9					+						98.6	104											
	9	Farrell	5		+					+		+		99.4	84						+					
	10	Port	47D					+						103.2	108					+						
	11	Weathers	4D											100.8	68						+					
	12	Lee	D					+						103.0	104								+			
	13	Greener	D			+		+						101.0	100					−		+				
	14	Gibson	3					0 +			+	+		100.0	100											
	15	Moseley	D					F+						98.0	100							+				
	16	Harmage	D											102.5	104											
	17	Page	D			−		+						98.2	106						+					
	18	Josey	4			+		+		+	+			101.2	90			+		+	+	+	+			
	19	Ward	D			+		+						103.6	100					+	−	−				
	20	Denson	D					+		+			+	98.8	100							+	+			
	21	Sumner	D					+					+	99.8	104											
	22	Fringer	23					+						101.6	76							+				+
	23	Matthews	7					0 +	+					99.0	80											
	24	Womack	14					+		−				100.8	88								+	+		
		Total		0	1	4	1	19	3	7	5	7	3			0	1	1	2	4	10	9	3	3	0	3	1
		Average	9											100.0	100												
B1a	1	Grisson	3			+		−						98.0	72					+		+				
	2	Fletcher	2		−			F −		+				103.0	94							+				
	3	Pierce	5			+		+		+				104.0	110					−						
	4	Crews	15					+		+	+			102.0	116								+			
	5	Williamson	3											98.0	76										+	
	6	Pennington	5					F+			+			98.8	84				+	+		+				
	7	Smith	2					F+		+				102.0	120											
		Total		0	1	2	0	6	1	4	1	0	0			0	0	1	0	3	0	3	1	1	1	0	0
		Average	4											102.0	100												

—CEREBROSPINAL MENINGITIS—(*Continued*)

Number Showing Important Complications									Serum Effects							Reflexes (On Admittance)											Misc.	
												Anaphylaxis	Rashes			Adenitis													
C. Paralysis, Ocular	D. Epididymitis	E. Pneumonia	F. Pleurisy	G. Pericarditis, Dry	G. Pericarditis, Fluid	H. Otitis Media	I. Others					Chill	Collapse	Dyspnea	Erythema	Urticaria	Other Rashes	Cervical	Inguinal	Epitrochlear	General	Neck Rigidity	Kernig	Brudzinski	Patellars	Achilles	Abdominal	Cremasteric	Biceps	Triceps	Babinski	Clonus	Photophobia	Herpes
Swelling optic disks																					++	++	....	++	....	++	++	R>L++	R>L	R>L	0		
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TABLE 3.—Data of 208 Cases of—

Class	No.	Name	Duration of Fever, Days	Developing During or After: A. Pneumonia	B. Mumps	C. Measles	D. Others	Symptoms During Onset and Course of Disease: 1. Headache	2. Nausea	3. Vomiting	4. Chills	5. Delirium	6. Convulsions	7. Fever, F.	8. Pulse	9. Arthritis	10. Coryza	11. Sorethroat	12. Pneumonia	13. Cough	14. Unconsciousness	15. Eruption	16. Backache	No. Showing Important Comp.: A. Panophthalmitis	B. Arthritis, Mono.	B. Arthritis, Poly.	C. Paralysis, elsewhere
B1b	1	Buzzard	5					F+						101.2	108												
	2	Letchworth	9					+	+	+	+			97.0	86												
	3	Brademeyer	7					F+		+	+			102.0	100												
	4	Millwood	3					F+						101.0	118							+					
	5	Stillwell	4					+		+				98.6	99										+		
		Total		0	0	0	0	5	1	4	2	0	0			0	0	0	0	0	0	2	1	0	1	0	0
		Average	5											101.0	100												
	1	Manley	21											99.6	120												
	2	Grubb	4											99.0	80												
	3	Spurlock	8					–	–					101.0	100			–									
	4	Packer	0					F+						99.0	66		+										
	5	Dukes	D								+			100.4	104			–		–							
		Total		0	0	0	0	3	1	1	1	0	0			0	2	2	0	1	0	0	0	0	0	0	0
		Average	10											100.0	100												
B2b	1	Wetmore	19					+				+		101.2	100							–					
	2	Blanchard	12					+						101.0	98					+							
	3	Coulter	14					+	–	+				99.2	68								+				
	4	Shafner	27					+			+			102.2	82						+			+			
	5	Benner	D					+			+			100.2	64												
	6	Murphy	D					+						101.8	110		+					+					
	7	Pope	D							–	+			101.8	100								–	+			
	8	Borden	19					–		–				98.2	88						+	+					
	9	Poole	D											101.0	96						+						
	10	Thomas	1		+									103.0	96			+				–					
	11	Dyer	D					–		+				101.4	102			+					+				
	12	Beasley	16					F–		+				97.4	84						+						
	13	Tanner	D									+		103.0	110						+						
	14	Smith	D					+			–			101.0	88		–	+		–							
	15	Chandler	D											98.2	88					+	+	+					
	16	Culpepper	D					F+						98.6	84						–						
	17	Anderson	D		–									100.0	100												
	18	White	D					F+			–			99.0	82							–	+				
	19	Castles	D											100.0	100							–					
	20	Adams	D											103.0							–						
		Total		0	1	1	0	12	1	6	5	2	0			0	2	3	0	3	10	10	6	2	1	0	0
		Average	10											99.0	90												
C1a	1	Fleming	2					–			–			100.2	104							–					
	2	Latham	5											98.0	80		–			–		–					
	3	Davis	7	+										101.0	98						+						
	4	Hilner	4					0+						100.0	126			–									
	5	Staley	8					+	+	+	–			101.2	80												
	6	Layton	3					+						98.2	76												
	7	Moore	6					T+		–	–			100.8	96												
	8	Thacker	15			+		+						100.4	74							–					Facial, left arm
	9	Galloway	6					+						101.0	110							–	+				
	10	Bray	4					F –			–			100.4	112							+					
		Total		1	0	1	0	8	1	3	4	0	0			0	1	1	0	1	1	5	1	0	0	0	1
		Average	6											100.5	100												
C1b	1	Breaux	19					F –			+			99.4	128						–	+	+				
	2	Carkhuff	4					+	+	+				101.0	120												
	3	Arrants	3					+		–	–			100.2	88												
	4	Fletcher	14					+		+				103.0	94						+						
		Total		0	0	0	0	4	2	3	2	0	0			0	0	0	0	0	2	1	1	0	0	0	0
		Average	10											101.0	100												

Number Showing Important Complications									Serum Effects						Reflexes (On Admittance)											Misc.
											Anaphylaxis	Rashes		Adenitis												
C. Paralysis, Ocular	D. Epididymitis	E. Pneumonia	F. Pleurisy	G. Pericarditis, Dry	G. Pericarditis, Fluid	H. Otitis Media	I. Others		Chill	Collapse	Dyspnea	Erythema	Urticaria	Other Rashes	General	Epitrochlear	Inguinal	Cervical	Neck Rigidity	Kernig	Brudzinski	Patellars	Achilles	Abdominal	Cremasteric	Biceps	Triceps	Babinski	Clonus	Photophobia	Herpes
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0	2	0	0	0	0	0	2																							
..	+	..	..	..	..	....	Mumps		..	..	..	..	..	..	..	..	..	+	+	....	....	....	....	....	.....	....	....	....	....	.
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0	1	0	0	0	0	0	1																							

Class	No.	Name	Duration of Fever, Days	Developing During or After: A. Pneumonia	B. Mumps	C. Measles	D. Others	Symptoms During Onset and Course of Disease: 1. Headache	2. Nausea	3. Vomiting	4. Chills	5. Delirium	6. Convulsions	7. Fever, F.	8. Pulse	9. Arthritis	10. Coryza	11. Sorethroat	12. Pneumonia	13. Cough	14. Unconsciousness	15. Eruption	16. Backache	No. Showing Important Comp.: A. Panophthalmitis	B. Arthritis, Mono.	B. Arthritis, Poly.	C. Paralysis, elsewhere
C2a	1	Merrill	3		+			0+			+			103.0	96						+						
	2	Nelson	2					F						104.0	108						+						
	3	Chastain	13					−	+	+	+			100.0	100							+					
	4	Jamieson	*					F+		+				100.0	100					+	+	+				+	
	5	McMillan	7					F+						102.0	112			+	+			+					
	6	Smith	?*									+		100.0	104						−						
	7	Letes	7					F+		+				97.4	62												
	8	Stewart	10					F+	+	+	+			99.8	92							+					
	9	Brumley	10					+		+				101.8	86					+		+					
	10	Foster	6					+		+	+			100.0	100						+						
	11	Jenkins	4					+		+	+			104.0	100												
	12	Thomas	D		+			+			+			99.0	74							+					
	13	Workman	D			−	Typhoid inoc.			+				102.0	98			+		+		+					
	14	Heath	5					+						103.0	84		+			+							
	15	Cloer	4					F+						101.0	90		+			+							
	16	Nelson	4					+						99.2	90					+							
	17	Stone	?					+						102.0	110			+				+					
		Total		0	2	1	1	15	2	9	6	1	0			0	2	3	1	6	5	8	0	0	0	1	0
		Average	6											101.0	95												
C2b	1	Johns	12					F+						100.0	80								+		+		
	2	Moninger	4					+		+	−		+	99.0	78							+	+	+			
	3	Veasey	22					+	+	+	+	−		98.0	72						+	+					
	4	Walker	*					+	+	+	+	+		101.2	88			Purpura			+	+			+		+
	5	Byrd	15					+				+		99.0	84						+						
	6	Le Fever	6					+	+	+				101.2	116												
	7	Rascoe	7					+		+		+		102.2	102							+					
	8	Cooper	8					+						99.8	96					+		+					
	9	Keeble	7					+	+	+				101.0	88												
	10	Wright	3								+			103.8	128		+			+							
	11	Robinson	*					F+	+	+				98.0	126						+	+				+	
	12	Perry	12					+						100.0	102						+						
	13	Stevenson	4					+						98.6	96						+						
	14	Lovelace	14		+		Otitis	1+		+				103.0	102												
	15	Cockerhan	D					F+						100.0	100								+	+			
	16	Runyam	D				Otitis				+			103.0	88												
	17	Romanquera	D											102.4	60						+	+					+
	18	Payne	D			+		F+						98.0	72								+				
	19	Hendrix	0	+			Otitis	+						103.0	96												
	20	Hampton	D								+			104.0	96			+		+							
	21	Frezevant	D					F+				+		100.0	80						+	+					
	22	Berry	D							−				98.0	60			+			+	+					
	23	Drane	21					+						102.2	96											+	
	24	Bell	19					+						101.4	92						+	+	+			+	
	25	Moss	45*					+	+	+				98.0	76			Lat. nyst.				+	+				
	26	Sanders	21					+			−			102.0	70			+	+				+	+		+	
	27	Little	1					F+		−				101.3	96												
	28	Armstrong	2		+			+	+	+				102.3	80							+					
	29	Arnold	9					+						102.0	100						+						
	30	Hanley	1									+		98.4	92						+						
	31	Scott	6					+		−		+		102.0	88					+	+						
	32	Davis	2					+						100.6	120			+		+		+					
	33	Shull	4					F+						100.0	64							+					
	34	Lynch	4		+			+	+	−				101.0	92					+	+						
	35	Lewis	5					F+	+	+				102.3	100		+			+		+					
	36	Holmes	2					+	+	+	+			102.0	90							+					
	37	Ingham	7					F−		+	+			103.2	101						+						
	38	Washington	5					F+			+		+	102.2	80						+						
	39	Wild	2					+	+					104.4	130						+	+					
	40	Black	7					+		+	+			101.2	108												
	41	Jenkins	13					F+		+	+			101.0	100							Peritonsillar abscess					
	42	Hackner	15					+		+				99.0	96							+	+				
	43	Kimball	D					+		−				100.0	110						+						
	44	Cross	3					−	+	+	−			103.4	90					+	+						
	45	Ross	17					+	+	+		+		103.4	92		+				+				+		
	46	Catron	17		+			+	−	−		+		105.0	102								+				
	47	Schwartzer	3					+	+	+	+			101.4	102								+				
	48	Chastant	?	+				F+	+	+	+	+	+	101.0	86					+	+	+	+				Right ulnar
		Total		2	4	1	3	42	19	26	16	11	3			0	3	4	2	9	22	17	12	3	3	4	2
		Average	10											101.5	90												

Number Showing Important Complications								Serum Effects						Reflexes (On Admittance)											Misc.
C. Paralysis, Ocular	D. Epididymitis	E. Pneumonia	F. Pleurisy	G. Pericarditis, Dry	G. Pericarditis, Fluid	H. Otitis Media	I. Others	Anaphylaxis	Rashes				Adenitis												
								Chill	Collapse	Dyspnea	Erythema	Urticaria	Other Rashes	Cervical	Inguinal	Epitrochlear	Parotid	Neck Rigidity	Kernig	Brudzinski	Patellars	Achilles	Abdominal	Cremasteric	Biceps	Triceps	Babinski	Clonus	Photophobia	Herpes
																		+	+	....	....	...	....	....	.....	....	....	..	..
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Cellulitis Erysipelas							+	–	+	–								++	++	....	++	..	....	....	.....	....	....	..	..
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Erysipelas							–											+	–	+	....	....	....	....	.....	....	....	..	–
																		+	+	+	....	....	....	....	.....	....	....	..	..
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0	0	1	1	0	0	1	2																						
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	+	–					Gangrene toes	–	+	+			–					- -	– –	....	....	....	....	....	.....	....	....	..	–
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							Mumps											++	++	++	+++	+	++	– –	++	– +	0	0	..
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Paralysis left arm																		+	....	....	....	....	....	....	.....	....	....	..	..
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							Erysipelas					+						++	++	....	....	....	....	....	.....	....	....	..	..
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Edema of retina																		+	+	–	....	....	....	....	.....	....	....	..	..
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																		+++	++	....	+	....	....	....	.....	....	....	..	..
Recurrence																		+	+	....	....	....	....	....	.....	....	....	..	..
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																		....	....	....	....	....	....	....	.....	....	....	..	..
																		+	0	....	++	+	....	....	.....	....	....	..	..
+																		– –	++	+	++	0	0	0	0	0	0	+	0
												–						+	+	+	0	0	+	+	0	0	–	0	+
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												+						++	+	– –	+	0	N	N	N	N	0	0	0
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												–						+	+	+	0	0	0	0	0	0	0	0	–
												–						++	++	+	0	0	0	0	0	0	0	0	+
Septicemia												–						+	+	+	++	0	0	0	0	0	0	0	–
												–						+	+	+	++	....	....	....	.....	....	....	..	+
paresis; recurrence; diabetes insipidus												–						+++	++	+	0	0	....	....	.....	....	....	..	–
3	2	2	2	2	0	2	2																						

TABLE 4.—Epidemic Cerebrospinal Meningitis. Summary of 208 Cases in Classes

Class	Cases	Development During or After: A. Pneumonia	B. Mumps	C. Measles	D. Others	Symptoms During Onset and Course of Disease: 1. Headache	2. Nausea	3. Vomiting	4. Chills	5. Delirium	6. Convulsions	7. Fever	8. Pulse	9. Arthritis	10. Coryza	11. Sorethroat	12. Pneumonia	13. Cough	14. Unconsciousness	15. Eruption	16. Backache	Number Showing Important Complications: A. Panophthalmitis	B. Arthritis, Mono.	B. Arthritis, Poly.	C. Paralysis, elsewhere	C. Paralysis, Ocular	D. Epididymitis	E. Pneumonia	F. Pleurisy	G. Pericarditis, Dry	G. Pericarditis, Fluid	H. Otitis Media	I. Others
A1a	36	2	2	6	4	28	3	11	10	0	0	101.0	90	1	2	7	1	0	2	6	9	0	0	3	1	0	0	3	2	0	0	4	1
A1b	17	0	3	5	1	17	4	8	5	1	1	100.4	90	0	0	1	0	0	1	9	3	0	0	0	0	1	1	0	0	0	1	2	0
A2a	15	0	1	5	0	10	0	2	2	5	0	102.5	95	0	2	2	0	4	8	7	7	1	0	0	0	0	0	4	0	0	0	0	0
A2b	24	0	1	4	1	19	3	7	5	7	3	100.0	100	0	1	1	2	4	10	9	3	3	0	3	1	1	2	2	0	0	0	3	0
B1a	7	0	1	2	0	6	1	4	1	0	0	102.0	100	0	0	1	0	3	0	3	1	1	1	0	0	0	0	0	0	0	0	1	0
B1b	5	0	0	0	0	5	1	4	2	0	0	101.0	100	0	0	0	0	0	0	2	1	0	1	0	0	1	0	0	0	0	0	0	0
B2a	5	0	0	0	0	3	1	1	1	0	0	100.0	100	0	2	2	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
B2b	20	0	1	1	0	12	1	6	5	2	0	99.0	90	0	2	3	0	3	9	9	6	2	1	0	0	1	1	2	0	0	0	3	0
C1a	10	1	0	1	0	8	1	3	4	0	0	100.5	100	0	1	1	0	1	1	5	1	0	0	0	1	0	2	0	0	0	0	0	2
C1b	4	0	0	0	0	1	2	3	2	0	0	101.0	100	0	0	0	0	0	2	1	1	0	0	0	0	0	1	0	0	0	0	0	1
C2a	17	0	2	1	1	15	2	9	6	1	0	101.0	95	0	2	3	1	6	5	8	0	0	0	1	0	0	0	1	1	0	0	1	2
C2b	48	2	4	1	3	42	19	26	16	11	3	101.5	90	0	3	4	2	9	22	17	12	3	3	4	2	3	2	2	2	2	0	2	2
Total	208	5	15	26	10	169	38	84	59	27	7	.....	...	1	15	25	6	31	60	76	44	10	6	11	5	7	9	15	5	2	1	16	8
Average	..	..	..	..	..	..	..	..	..	..	..	101.0	96																				

tenant Cobb's method when drainage is slight and symptoms persist with occasional intravenous injections of serum have given us the most satisfactory results in these difficult cases.

It has not been found necessary to follow the blood pressure either during withdrawal of spinal fluid or while giving serum intraspinally. In many hundred lumbar punctures and serum treatments no serious symptoms were observed. The well known serum effects were noted but do not require description. Only one case showed serious anaphylaxis.

Visitors to the wards where the patients are treated by the methods described remark on the absence of delirium and of the lack of subacute and chronic cases with cachexia, delirium, hydrocephalic cries and the distressing picture of the prolonged cases. In a large number the nutrition suffers little. Some patients with stormy onset ask to be allowed up and about on the fourth day. There is an air of cheerfulness and optimism about the patients, reminding one of a convalescent surgical ward. The proof of the value of this therapy is found in the shortened course, the diminished number of complications, the greater comfort of the patients, the prompt disappearance of meningococci from the spinal fluid and the decreased mortality.

CONCLUSIONS

1. A camp epidemic of 208 cases of cerebrospinal meningitis is reported.

2. The disease is in most, probably in all, instances a primary meningococcus sepsis with usual, but not necessarily universal, secondary meningitis.

3. The diagnosis can be made in at least 50 per cent. of the cases in the premeningitic stage of sepsis.

4. Treatment by large amounts of antimeningococcus serum intravenously, combined with active spinal drainage and intraspinal serum administration, has reduced the duration of the disease, the number and severity of complications and the mortality.

Acknowledgment is heartily given Capt. F. W. Baeslack, M. R. C., who with his staff has done invaluable work in the laboratory without which the clinical work of this epidemic could not have been carried out. Captain Baeslack's important contribution will be reported separately.[5]

Capt. George A. Blakeslee, M. R. C., has made neurologic observations, the necropsies, and has had general supervision of therapy. To his careful attention to details and valuable suggestion much of the therapeutic success is due. A separate report of the neurologic aspect of the epidemic will be made by him.

To the officers who from time to time have served on the Meningitis Squad acknowledgment of skilled and devoted service is made, Capts. D. L. Walker, H. S. Fincke and E. W. Barron; First Lieuts. B. Lattin, G. M. Parkhurst, Q. H. Barney, A. M. Dannenburg, L. H. Taft, F. W. Rogers, R. C. Davis, S. A. Cobb.

I am indebted to S. A. Cobb and R. C. Davis, First Lieutenants, M. R. C., for the accompanying tabulation of the epidemic.

BOOK REVIEW

BOOK REVIEW: A TEXTBOOK OF THE PRACTICE OF MEDICINE, by James M. Anders, M.D., Ph.D., LL.D., Professor of Medicine and Clinical Medicine, Medico-Chirurgical College Graduate School, University of Pennsylvania, Thirteenth Edition Thoroughly Revised with the Assistance of John H. Musser, Jr., M.D., Associate in Medicine, University of Pennsylvania. Octavo of 1259 pages, fully illustrated. Philadelphia and London: W. B. Saunders Company, 1917. Cloth, $6.00 net; Half Morocco, $7.50 net.

This is essentially a textbook of internal medicine and diagnosis and as such will be welcomed by both medical students and practitioners.

The present, thirteenth, edition has been thoroughly revised, and several subjects entirely rewritten; and the presence of a thirteenth edition is sufficient to prove that it has met the requirements of the profession. In general the work is carefully compiled and up to date, convenient for reference and presents the material in an accessible form; being concise, and at the same time sufficiently elaborate for students.

The authors have been successful in their effort to correlate pathology and morbid physiology with the clinical and therapeutic aspects of disease and throughout the book emphasized the necessity of recognizing the interdependence of the two phases. In addition to a section on "Diseases of the Nervous System," there has been added a wealth of modern material on focal infection, kidney function tests, asthma, acidosis in diabetes, anaphylaxis of food and many other subjects.

Particularly useful are the diagnostic tables with the stated aim of giving a practical working knowledge of contrasting features that present points of similarity at the bedside. The authors further emphasize the difference between causal and symptomatic treatment of disease, recognizing the importance of each, yet maintaining a distinction between the two.

The subject matter is arranged in systems, as Infectious Diseases, Diseases of Metabolism, Diseases of the Respiratory System, etc., and each topic is discussed under the headings of Definition, Pathology, Etiology, Clinical History, Complications, Diagnosis and Differential Diagnosis, and Treatment, with numerous historical notes.

The plates, charts and illustrations are good but rather meager, and while a work of this sort cannot be profusely illustrated, there are many points at which an added illustration would be of great assistance to the student. Nothing has been overlooked to make the book thorough and accessible, even to anticipating the student's habit of underlining by very successfully italicizing the key words throughout.

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